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CLINICAL TRIALS

1. EFFICACY OF BCG ADJUVANT THERAPY IN BREAST CANCER (MEETING ABSTRACT).

Serrou B, Pujol H, Gary-Bobo J, Cupissol D
Department of Radiotherapy, Centre Paul Lamarque, Hopital St-Eloi, B.P. 5054, 34033 Montpellier, Cedex, France
4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

One hundred breast cancer patients (T1-T3, N0-N1b) were treated by irradiation followed by randomization into two groups: 1) no adjunct treatment; or 2) 150 mg Immun-BCG-F (Pasteur Institute) po, once a wk for 1 yr. The study has since ended and all patients have been followed for at least 15 mo. No side effects were observed for BCG (vomiting, diarrhea, etc) necessitating cessation of treatment. After 3 yr the BCG group shows 26.2% relapse and no mortality compared to 58.3% relapse in the control group and 1 death. Moreover, the BCG group demonstrated a significant immunorestoration: delayed hypersensitivity skin tests; auto-rosette forming cells; natural killer activity; anti-BCG antibodies. The 26% relapse in the BCG group was comparable in type of metastasis to the

HE 20. 3173/2:

control group. These favorable, significant results suggest a useful role for oral BCG therapy to stimulate restoration of immune functions in irradiation-dependent immunodepressed cancer patients. Furthermore this therapy is well tolerated by the patient. (no Refs)

2. THE IMMUNOTHERAPY OF LUNG CANCER.

Holmes EC
Div. Surgical Oncology, UCLA Sch. Medicine, 54-140 CHS, Los Angeles, CA, 90024
Cancer Treat Res; 1:51-62 1981

Clinical trials of nonspecific immunotherapy with BCG or Levamisole as surgical adjuvants in lung cancer and of specific immunotherapy with tumor antigens are summarized. The efficacy of Levamisole has not been established, but BCG treatment has resulted in a significant increase in the disease-free interval in patients with resected Stage I lung cancer. Preliminary findings of a Phase II study of intralesional BCG injections followed by resection indicated that the treatment prolonged survival and increased the functional activity of the lymphocytes infiltrating the injected tumor. (29 Refs)

3. CHEMO-IMMUNOTHERAPY ADJUVANT TREATMENT (DTIC AND BCG) OF STAGE I AND II MALIGNANT MELANOMA (MEETING ABSTRACT).

Comella G, De Simmone G, Castello G, Iazzetta A, Comella P, DeMarco MR, Cerra R, Zarrilli D
No affiliation given
Tumori; 67(2,SupplA):209 1981

From January, 1977 to December, 1980, 44 patients with stage I and II (lymph node involvement) malignant melanoma underwent chemotherapy with dacarbazine (DTIC) in a dose of 200-250 mg/square m iv for 5 days every 4 wk for a total of 12 cycles and immunotherapy with Berna BCG (10 IU) one vial per day id, once a wk for 3 yr following surgery consisting of wide excision of the primary lesion and initial lymph node excision for sites in the extremities. 75 per cent of the patients are alive and disease-free after 4 yr; in particular 83 per cent of patients in stage I (none with evidence of disease) and 64 per cent of patients in stage II (49 per cent disease-free) are still living; these differences are not statistically significant. Out of 13 patients in stage I and Clark's level III, 10 are alive and free of disease; of 14 patients in stage I and Clark's level IV, all are alive and 12 are free of disease. By comparing our results with those of other authors we can conclude that chemotherapy is capable of improving survival and d isease-free intervals in stage II patients and that, in addition, there are no prognostic differences between patients with Clark's level III or IV. (no Refs) (In ITA)

4. CONTROLLED STUDY OF ADJUVANT THERAPY OF STAGE I MALIGNANT MELANOMA: SURGERY VS SURGERY PLUS PROLONGED IMMUNOSTIMULATION WITH BCG (MEETING ABSTRACT).

Canaletti R, Nouvenne R, Marola G, Rossi G, Sturba F, Bachetti G, Piva G, Pezzarossa G, Moroni P, Bonsignori M
Centro Medico Oncologico, Ospedali Riuniti, Parma, Italy
Tumori; 67(2,SupplA):89 1981

Patients with melanoma of the limbs, head and neck were admitted to the study; Clark level between 3 and 5; absence of regional and/or distant lymph node metastases. Following wide excision of the lesion performed within 4 wk, the patients were randomized into 2 groups: a) immunostimulation with BCG, b) no treatment (controls). BCG treatment was continued for 2 yr, however it was interrupted when the disease recurred. From June, 1975, till April, 1980 (the study is still in progress), 67 patients were admitted to the study 66 of whom are evaluable, 32 in the control group and 54 in the experimental group. The actuarial curves for free interval reveal a higher recurrence rate in the control group than the experimental group (p, 0.07). The median disease-free interval, estimated from an actuarial curve projection is 95 wk in the control group and 326 in the experimental group (p, 0.004). It is concluded that the study demonstrates the usefulness of BCG stimulation in melanomas of the limbs, head and neck. (no Refs) (In ITA)

5. INTRAPERITONEAL ADMINISTRATION OF CORYNEBACTERIUM PARVUM IN PATIENTS WITH OVARIAN TUMORS: EFFECTS ON THE CYTOTOXICITY OF MACROPHAGES AND NK CELLS ASSOCIATED WITH THE TUMOR (MEETING ABSTRACT).

AllavenaP, Sessa C, Introna M, Peri G, Polentarutti N, Molina P, Mangioni C, Mantovani A
Clinico Ostetrico-Ginecologica Universita, Milan, Italy
Tumori; 67(2,SupplA):113 1981

Eight patients with ascitogenic carcinoma of the ovary, resistant to various chemotherapy protocols, were treated with ip Corynebacterium parvum in an attempt to reduce the amount of peritoneal effusion. C parvum (7-14 mg) was administered ip on days 0, 7, and 28 and at monthly intervals thereafter. 3 patients showed no clinical improvement after taking C parvum. In 3 patients there was complete disappearance of their ascites, while another 2 patients showed a net reduction in their effusions. Solid tumor masses were unchanged after treatment with C parvum, but the number of tumor cells present in ascitic fluid was considerably reduced after only 7-15 days after the first infusion; there was a simultaneous increase in the percentage of polymorphonuclears, and to a lesser extent, of macrophages (TAM), whereas the number of lymphoid cells (TAL) appeared not to have changed. The tumoricidal activity of monocytes and Natural Killer (NK) cells in the peripheral blood was not altered in a consistent fashion. The NK activity of lymphoid cells in ascites was generally low when tested before treatment and did not change appreciably following C parvum treatment. The tumoricidal activity of TAM underwent a net reduction 14-21 days after the first inoculation with C parvum and later returned to pretreatment levels. The mechanism of the limited antineoplastic activity of C parvum in these patients awaits clarification. The lack of stimulation of cytotoxicity of macrophages and NK cells, anticipated as a result of the experimental results, is a warning against the empirical utilization of immunostimulating compounds. (no Refs) (In ITA)

6. EFFECT OF INTERFERON IN THERAPY OF SKIN AND HEAD AND NECK TUMORS.

Padovan I, Brodarec I, Ikic D, Knezevic M, Soos E
(c/o Ikic) Inst. Immunology, Zagreb, Yugoslavia
J Cancer Res Clin Oncol; 100(3):295-310 1981

The use of human leukocyte interferon (HLI) for treatment of 30 patients (12 females, 18 males; aged 44-91 yr) with skin cancers (3 on cheek and chin, 5 on lower lip, 7 on nose, 4 on forehead, 3 on ear shell, 2 on skin of the neck) and tonsil cancer (3 cases), tongue cancer (1), and benign tumor (1), is reported. The duration of treatment was 1-6 mo and HLI was administered in the form of infiltration injections into the tumor or its immediate vicinity. During the first 7-19 days HLI was administered daily, thereafter it was given 2-3 x/wk. A single daily dose was 3 x 10(5) units of crude, unpurified HLI. Histologically, there were 13 cases of squamous cell carcinoma, 15 of basocellular carcinoma, one case of neurogenic sarcoma, and one of benign skin tumor. Clinical results were excellent in 10 patients, very good in 10, satisfactory in 5, hardly effective in 2, and not effective in 3. Immunological testing revealed excellent results in nine, very good results in three, satisfactory results in four, hardly effective results in two, no effect in three, and tests were not performed in nine. HLI reduced the biologic potential of the infiltrative tumor growth and caused solidification of the basic tissue and proliferation of connective tissue, thus obstructing infiltrative growth and the possibility of metastases. (20 Refs)

7. CLINICAL EXPERIENCES WITH HUMAN FIBROBLAST INTERFERON.

Furue H, Komita T, Kobayashi H, Hakozaki M, Kondo S, Tajima S
Second Dept. Internal Medicine, Teikyo Univ. Sch. Medicine, Sagamiko-machi, Kanagawa Prefecture 199-01, Japan
Nippon Gan Chiryo Gakkai Shi; 16(2):220-228 1981

Results of administration of human fibroblast cell interferon (IF) to 16 patients with advanced cancer and 1 patient with B-type hepatitis were discussed. IF was administered in doses of 1-3 million units/day or 2-3x/wk. Levels of serum IF varied with the route of administration. Serum IF activity dropped rapidly following iv administration of the IF: serum levels dropped 20 min after one shot administration, and after iv drip infusion, levels dropped to half 60 min later and to zero 6 hr later. IF was not detectable in the serum of patients given im injections of IF. Complete recovery was observed in one 5-yr-old girl who had acute myelogenous leukemia; the patient received a total of 3.1 x 10(6)/kg units of IF after being refractory to other anticancer drugs. Three of seven patients who received combination chemotherapy and IF had complete remission. Side effects included transient fever with or without chills and neuralgic pain. These results indicated that further therapeutic trials should be performed. (36 Refs) (In JPN)

8. PRELIMINARY PHASE I STUDY OF HUMAN LEUKOCYTE INTERFERON: SIDE EFFECTS OF THE INTERFERON.

Imanishi J, Ito H, Murakami K, Sawada T, Kishida T
Dept. Microbiology, Kyoto Prefectural Univ. Medicine, Kawaramachi-Hirokoji, Kamikyo-ku, Kyoto 602, Japan
Jpn J Clin Oncol; 11(1):9-14 1981

The side effects of systemic administration of human WBC interferon (IF) to 11 patients with cancer and 2 patients with viral infections were examined. After purification, the specific activity of the IF was about 3 to 10 x 10(5) IU/mg of protein. When IF was injected im, the body temperature of all of the patients increased by various amounts over time, reaching a max at between 3-6 hr after injection. Iv IF generally caused a more rapid rise in body temperature than did im IF. With repeated im or iv IF administration, the max temperature was gradually reduced. During long-term administration of IF, an increase in WBC, mainly neutrophils, was observed in six patients, with no evidence of infection. A mild transient anemia was seen in two patients with primary lung cancer. IF produced no marked changes in the bone marrow of the three patients with primary lung cancer so examined. IF did not appear to affect the function of the kidney, liver, or pancreas as indicated by biochemical tests. The results indicated that IF does not produce severe irreversible side effects. (18 Refs)

9. A PHASE I STUDY OF 5 BIOLOGICAL RESPONSE MODIFIERS (BRM) IN IMMUNODEPRESSED SOLID TUMOR BEARING PATIENTS (MEETING ABSTRACT).

Serrou B, Cupissol D, Favier F, Rosenfeld C
No affiliation given
Immunobiol; 159(1/2):100 1981

Many recent data suggest that non immunodepressed patients respond better to chemotherapy than immunodepressed patients. This fact, closely related to the immune imbalance of the cancer patient, of itself justifies the recent interest in BRM. In a phase I study in immunodepressed solid tumor bearing patients, we evaluated the immunorestorative potential of 5 BRM: human fibroblast interferon (HFIF) injected IV: Bestatin purified from Streptomyces olivoreticuli: NPT 95 392 which is a new Isoprinosine derivative; RO 95132 a retinoic acid derivative and Cyclomunine purified from Fusarium equiseti. These BRM were used for 3 wk and all parameters were evaluated before and after treatment. At the doses used, no BRM presented major side-effects (hepatic or renal dysfunction, blood pressure, cardiac function, hematological modification). Effects on delayed hypersensitivity responses as evaluated by the Merieux skin test scores, evaluation of T cell subsets responding in autologous MLC and natural killer (NK) activity showed significant changes for all drugs, although NK activity significantly increased only after HFIF and Bestatin. These results underline the increasing attention being given to these BRM which are now just entering phase 3 studies as adjuvant therapy (Bestatin), or phase 2 studies either alone (HFIF) or associated with chemotherapy. (no Refs)

SYNTHETIC IMMUNOTHERAPEUTIC AGENTS

10. ACTIVATION OF MACROPHAGES FOR TUMOR CELL CYTOTOXICITY: IDENTIFICATION OF INDOMETHACIN SENSITIVE AND INSENSITIVE PATHWAYS.

Drysdale BE, Shin HS
Dept. Microbiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
J Immunol; 127(2):760-765 1981

Macrophages can be activated for tumor cell cytotoxicity by endotoxin- or lymphokine-containing soln, and in both cases 37 activation can be blocked by the addition of indomethacin. In contrast, the activation of macrophages by nonadherent or inflammatory peritoneal cells or antibody-coated tumor cells is not affected by indomethacin. These results demonstrate that there are at least two distinct pathways of macrophage activation, only one of which is affected by the addition of the drug. Activation by endotoxin that is indomethacin sensitive requires two steps. At present, the first is undefined and not blocked by indomethacin, but the second is inhibited by the drug and appears to require the production of E series prostaglandins. Our results also suggest that neither step alone is sufficient to activate macrophages for cytotoxicity. (Author abstract) (38 Refs)

11. INHIBITION OF TUMOR GROWTH BY COMBINED TREATMENT WITH CYCLOPHOSPHAMIDE (CY) AND POLYADENYLIC AND POLYURIDYLIC ACID (POLY (A):POLY (U)) IN C3H MICE BEARING A TRANSPLANTABLE MAMMARY TUMOR (MEETING ABSTRACT).

Lacour F, Youn JK, Hue G

Institut Gustave-Roussy, 94800 Villejuif, France

4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

The inhibition of tumor growth by CY administered sequentially in association with immunomodulators, POLY (A): POLY (U) or BCG, was studied in C3H mice bearing a transplantable syngeneic mammary tumor. A total of 212 mice were inoculated at Day 0 with 10(6) tumor cells. At Day 14 when their tumors attained palpable size, they received either 4 fortnightly inoculations of CY (90 mg/kg) alone or alternate weekly inoculations of the same doses of CY and POLY (A). POLY (U) (300 or 600 ug) or BCG (400 ug) during 8 consecutive wk. At Day 170, the following results were obtained. 1) Mice received either POLY (A): POLY (U) or BCG alone showed as rapid growth of tumor as observed in control untreated tumor bearers. 2) Mice received CY alone showed significantly delayed tumor growth and only 2 mice out of 34 (6%) were tumor free. 3) The most significant inhibitory effect was observed in mice received combined CY and POLY (A): POLY (U): 11 mice out of 44 (25%) were tumor free and tumor sizes of tumor bearers at Day 65 were less than half of those of mice receiving CY alone (mean diameter of 2.2 mm instead of 6.0 mm. 4) No such synergistic inhibitory effect was observed in mice that received combined CY and BCG. These results indicate that POLY (A): POLY (U) combined with a non toxic dose of cytostatic agent significantly improved the results obtained with the drug alone. (no Refs)

12. SUCCESSFUL TUMOR IMMUNOTHERAPY WITH CIMETIDINE BY ABROGATION OF SUPPRESSOR CELLS (MEETING ABSTRACT).

Osband ME, Lavin P, Brown A, McCaffrey R

Boston University Medical Center, Boston, MA, 02115

Pediatr Res; 15(4,Part2):583 1981

Immunotherapy has generally been aimed at stimulation of the patient's anti-tumor immune response. Since tumor growth may be associated with development of suppressor cells which could undermine an otherwise effective anti-tumor immune response, we have reasoned that an alternative immunotherapeutic strategy is the inactivation of suppressor cells by pharmacologic means, thereby allowing a more effective host anti-tumor immune response. Suppressor cells have a histamine H2 receptor on their surface which can be blocked by the H2 antagonist cimetidine (C). We therefore studied the effect of C on 3LL tumor in C57B1/6 mice. Tumors were allowed to grow until 7.5 mm at which time they were surgically removed, and mice were randomized to control or C groups. The latter received C in their drinking water at 0.2, 2.0 or 10.0 mg/ml. The mice receiving 10 mg/ml C had a significant decrease in metastatic development. C at all three dosages produced a significant prolongation in survival. These effects were associated with suppressor cell inactivation. We conclude that C allows metastatic development and prolongs survival by abrogation of suppressor cells. This suggests that a similar immunotherapeutic approach in human neoplasia is appropriate. (no Refs)

13. IMMUNOPOTENTIATING EFFECT OF VINCA ALKALOIDS ON THE ANTIBODY RESPONSE TO SHEEP RED BLOOD CELLS IN THE MOUSE.

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J Natl Med Assoc; 73(8):707-709 1981

Evidence is presented that the vinca alkaloids (vinblastine, vincristine, and vindesine) exert an immunopotentiating effect on the antibody response to sheep RBC (SRBC). The primary antibody response, measured by the rosette-forming cell and hemagglutination assays, was enhanced by vincristine and vindesine treatments. Neither drug had any effect on the secondary antibody response. Vinblastine, while having no effect on the primary response, augmented the secondary antibody response to SRBC. (Author abstract) (5 Refs)

INTERFERON

14. IN VITRO INHIBITORY EFFECT OF INTERFERON ON DNA SYNTHESIS OF BREAST CANCER CELLS AND RELATIONSHIP TO STEROID RECEPTORS (MEETING ABSTRACT).

Jakesz R, Kerjaschki D, Kolb R, Reiner G, Spona J, Swetly P

1st Surgical University Clinic, University of Vienna, Alserstrasse 4, A-1090 Vienna 9, Austria

Eur Surg Res; 13(1):31 1981

Apart from antiviral activity, interferon inhibits the growth of a number of tumors in vivo and in vitro. This effect is mediated partly due to a direct effect on tumor cell proliferation and partly due to an activation of immunological factors such as natural killer cells. For selecting patients for postoperative interferon treatment we carried out the following in vitro study. From 22 patients with primary or recurrent breast cancer, fresh tumor tissue was obtained. Tissue cultures were prepared from mouse bone marrow cells according to the method of Dexter et al and used as a feeder layer for cultivation of breast cancer cells in a humified atmosphere. At least 48 hr after incubation, confluent tumor cell colonies could be determined and the cells could be differentiated as epithelial using electron microscopy. For determining the influence of interferon DNA synthesis 3H-thymidine uptake was measured after incubation of breast cancer cells with interferon or without for control. 48 hr after incubation with interferon 3H-thymidine was measured. The results were expressed as percentage of inhibition of 3H-thymidine uptake compared with untreated controls. Three groups were divided: I greater than 80%, II 50-80%; III 0-49% inhibition. (1) An optimal reduction of DNA synthesis could be achieved in 32% with 100 U/human fibroblast interferon (HFI) and in 62% with the same dose of human lymphoblast interferon (HLI). (2) Using only 10 U interferon, only suboptimal reductions were seen. (3) 22% of ER+ culture cells show a marked reduction of DNA synthesis compared with 50% ER cells. These results indicate that 100 U HLI is more effective than the same dose of HFI. The higher response rate of cells or ER tumors could be an argument for selecting ER patients for interferon therapy. (5 Refs)

15. DIFFERENTIAL EFFECT OF INTERFERON ON THE EXPRESSION OF TUMOR-ASSOCIATED ANTIGENS AND HISTOCOMPATIBILITY ANTIGENS ON HUMAN MELANOMA CELLS: RELATIONSHIP TO SUSCEPTIBILITY TO IMMUNE LYSIS MEDIATED BY MONOCLONAL ANTIBODIES.

Imai K, Ng AK, Glassy MC, Ferrone F
Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, 10666 North Torrey Pines Road, La Jolla, CA, 92037
J Immunol; 127(2):505-509 1981

Incubation of cultured human melanoma cells with human leukocyte interferon did not change the expression melanoma-associated antigens (MAA) recognized by monoclonal antibodies and of Ia-like antigens but significantly increased the expression of HLA-A,B antigens and Beta2-microglobulin (B2-u). The effect is dependent on the dose of interferon and on the incubation time. Interferon-treated melanoma cells showed an increased susceptibility to lysis mediated by monoclonal antibodies to HLA-A,B antigens and to human B2-u; on the other hand, interferon-treated melanoma cells did not change in their susceptibility to murine natural (NK) cell lysis and to immune lysis mediated by monoclonal antibodies to MAA and to Ia-like antigens, and they displayed a reduced susceptibility to human NK cell lysis. Therefore, the increased susceptibility of interferon-treated melanoma cells to lysis mediated by anti HLA-A,B and anti B2-u monoclonal antibodies is likely to reflect the increase in cell surface expression of the corresponding antigens. (Author abstract) (29 Refs)

16. TUMORICIDAL ACTIVITY OF MACROPHAGES ISOLATED FROM HUMAN ASCITIC AND SOLID OVARIAN CARCINOMAS: AUGMENTATION BY INTERFERON, LYMPHOKINES AND ENDOTOXIN.

Peri G, Polentarutti N, Sessa C, Mangioni C, Mantovani A
Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea, 62 - 20157 Milan, Italy
Int J Cancer; 28(2):143-152 1981

Peripheral blood monocytes and macrophages from ascitic or solid tumors were obtained from 50 patients with advanced (Stage III or IV) ovarian carcinoma. Blood monocytes and peritoneal macrophages from 76 patients undergoing surgery for benign gynecological diseases were used as controls. Macrophages were 30% (range 0.2-62) and 2% (range 0.2-4) of mononuclear cell suspensions from ascitic and solid tumors, respectively. Cytolytic activity was measured as release of [3H]-thymidine from prelabeled mKSATU5 (TU5) target cells at an effector to target cell ratio of 20:1. Peripheral blood monocytes and tumor-associated macrophages had baseline cytotoxicity lower than or similar to that of control peripheral blood and peritoneal macrophages respectively. In vitro exposure to partially purified human fibroblast interferon, lymphokine supernatants or endotoxin augmented the cytotoxicity of mononuclear phagocytes, and no significant difference was observed between control and ovarian cancer effector cells from peritoneal effusions. In four patients, macrophages were isolated from the solid tumor or from the malignant effusion and tested in parallel: in two out of four subjects, macrophages from the solid neoplasm showed defective cytotoxicity compared to ascites effector cells from the same subject. When primary ovarian carcinoma cultures were used as targets, tumor cells from two out of five patients tested were relatively resistant to activated macrophage cytotoxicity. Thus, tumor-associated macrophages from ascitic or solid ovarian neoplasms showed no evidence of activation, in terms of spontaneous cytotoxicity or responsiveness to stimuli: it appears unlikely that small numbers of nonactivated macrophages present within primary ovarian carcinomas act as a significant mechanism of restraint of neoplastic growth, at least at this anatomical site. (Author abstract) (48 Refs)

17. MECHANISM OF INTERFERON ACTION. INHIBITION OF PPPA(2'P5'A)N-DEPENDENT RIBONUCLEASE ACTIVITY IN MICROCOCCAL NUCLEASE-TREATED MOUSE L CELL-FREE EXTRACTS.

Miyamoto NG, Samuel CE
Section Biochemistry and Molecular Biology, Dept. Biological Sciences, Univ. California, Santa Barbara, CA, 93106
Biochem Biophys Res Commun; 101(2):680-688 1981

The molecular basis by which the pppA(2'p5'A)n-dependent ribonuclease activity is blocked in micrococcal nuclease-treated as compared to nonpreincubated cell-free extracts prepared from interferon (IF)-treated mouse L cells was investigated. The micrococcal nuclease was purified from the Foggi strain of Staphylococcus aureus. Nonpreincubated and micrococcal nuclease-treated cell-free S-10 extracts were prepared from mouse L fibroblast cells grown in suspension culture. The mouse L cell-free extracts were supplemented with 2'-deoxythymidine-3',5'-diphosphate (pTp) and ethyleneglycol-bis(beta-aminoethyl ether)-N,N'-tetraacetic acid (EGTA) to catalyze the 2'-5'-oligo A tetramer enhanced degradation of reovirus [3H] messenger (m)RNA. Results indicated that (1) digestion of endogenous cellular RNA by the micrococcal nuclease during the preparation of the mRNA-dependent protein synthesizing system is required to establish the apparent inhibition of the 2',5'-oligo A-dependent ribonuclease, and (2) neither pTp nor EGTA directly affected the activity of either the 2',5'-oligo A synthetase or the 2',5'-oligo A-dependent ribonuclease in mouse L cells. (18 Refs)

18. AUGMENTATION OF NATURAL KILLER CELLS INVOLVES BOTH ENHANCEMENT OF LYTIC MACHINERY AND EXPRESSION OF NEW RECEPTORS.

Gustafsson A, Lundgren E
Dept. Clinical Virology, Univ. Umea, S-901 85 Umea, Sweden
Cell Immunol; 62(2):367-376 1981

A good correlation was found between the sensitivity of six hematopoietic cell lines to natural killing by both unstimulated and interferon (IFN)-stimulated effector cells and the ability of these cell lines to induce interferon among human WBC. Two cell lines (HL 60 and P3HR1) were not sensitive to natural killing by unstimulated effectors (less than 10 lytic units) and did not induce IFN. Augmentation of natural killing by preincubation of effector cells with IFN was found to alter the binding of lymphocytes to HL 60 cells but not K 562 cells. This indicates that the augmentation of natural killer cells by IFN involves both enhancement of the lytic machinery and development of new receptors. (Author abstract) (26 Refs)

19. INTERFERON ENHANCES THE AMOUNT OF MEMBRANE-BOUND BETA2-MICROGLOBULIN AND ITS RELEASE FROM HUMAN BURKITT CELLS.

Fellous M, Bono R, Hyafil F, Gresser I
Groupe de Recherches d'Immunogenetiques de la Transplantation Humaine, INSERM U 93, Hopital Saint-Louis, 2, Place du Dr. Fournier, F75475 Paris Cedex 10, France
Eur J Immunol; 11(6):524-526 1981

Human leukocyte interferon (HuIFN-alpha) increased the amount of beta2-microglobulin on the surface of human Burkitt lymphoma cells (Ramos) and also increased the amount released into the culture medium. The effect was observed 1 hr after addition of IFN. These results suggest that the increase in beta2-microglobulin on the cell surface of IFN-treated cells is not due to a decreased shedding of antigen from the cell surface, nor an 'unmasking' of surface antigen, but rather to an increased synthesis of antigen. (Author abstract) (38 Refs)

20. REVERSIBILITY OF THE TRANSFORMED AND NEOPLASTIC PHENOTYPE. I. PROGRESSIVE REVERSION OF THE PHENOTYPE OF X-RAY-TRANSFORMED C3H/10T1/2 CELLS UNDER PROLONGED TREATMENT WITH INTERFERON.

Brouty-Boye D, Gresser I
Institut de Recherches Scientifiques sur le Cancer, BP 8, 94802 Villejuif, France
Int J Cancer; 28(2):165-173 1981

X-ray transformed mouse C3H/10T1/2 cells were cultivated and passaged in the continuous presence of partially purified mouse interferon. This prolonged interferon treatment resulted in a stepwise progressive reversion of the transformed phenotype to the non-transformed phenotype. Thus interferon-treated cells displayed an epithelioid morphology, grew to a lower cell density, and were no longer tumorigenic. Reversion to the non-transformed phenotype was, however, stable only as long as interferon was continuously present in the culture medium. When interferon was removed, the cells 'back reverted' to the transformed phenotype. Our results suggest that interferon induced a reversion of the transformed phenotype in the entire cell population rather than a selection of an interferon resistant cell population. C-type viral particles and significant levels of reverse transcriptase were present in transformed cells, but neither were present in the parental 10T1/2 cells nor in interferon-treated cells. When interferon was removed from the culture medium, viral particles and reverse transcriptase activity were again detected. It is possible, therefore, that interferon induces reversion through its antiviral activity, or that it induces reversion by its effects on cell function and structure, independently of any antiviral effect. Inhibition of cell multiplication per se does not appear to be sufficient to induce reversion, since cycloheximide inhibited cell multiplication; however, even after ten passages, it did not affect tumorigenicity. Our results suggest the possibility that interferon may act in vivo not only by inhibiting tumor cell multiplication but also by inducing a reversion. Patients with some tumors may therefore benefit from long-term interferon treatment. (Author abstract) (24 Refs)

21. SEQUENTIAL PRODUCTION OF IFN-ALPHA AND IMMUNE-SPECIFIC INF-GAMMA BY HUMAN MONONUCLEAR LEUKOCYTES EXPOSED TO HERPES SIMPLEX VIRUS.

Green JA, Yeh TJ, Overall JC
Div. Infectious Diseases, Dept. Internal Medicine, Univ. Utah Coll Medicine, 50 North Medical Drive, Salt Lake City, UT, 84132
J Immunol; 127(3):1192-1196 1981

Both viral-induced interferon (IFN-alpha) and immune interferon (IFN-gamma) were produced in cultures of human peripheral mononuclear leukocytes (PML) exposed to UV light-inactivated herpes simplex virus (HSV). Comparable IFN titers (100 to 300 U) were present in supernatant media from PML of HSV-seropositive and -seronegative donors maintained for 2 days in culture. This 'early' IFN was not immunologically specific and had the characteristics of IFN-alpha. In contrast, PML from 20 of 21 (95%) seropositive donors, but only 2 of 22 (9%) seronegative subjects, produced IFN in day-5 cultures that had been washed on day 2 followed by the addition of fresh media without UV-HSV (p less than 0.0001). In addition, the geometric mean IFN titer of 35 U present in media from day 5 cultures of seropositive donors was significantly higher (p less than 0.0001) than those from seronegative subjects (less than 10 IFN U). This 'late' IFN was defined as immunologically specific by virtue of its being present almost exclusively in PML cultures from seropositive donors. Late-appearing, HSV-induced, immunospecific IFN-gamma had antigenic characteristics of both viral-induced IFN-alpha and mitogen-induced IFN-gamma. A considerable degree of overlapping sensitivity to anti-IFN-alpha and anti-IFN-gamma antibody existed in late IFN, but was not seen in standard, control specimens. The latter finding suggests that the possible existence of an IFN of antigenic character intermediate to IFN-alpha and IFN-gamma. Late IFN was not induced in PML cultures by UV-inactivated Newcastle disease virus (NDV). NDV did, however, induce high titers of early IFN-alpha in PML cultures of both HSV-seropositive and HSV-seronegative donors. HSV-stimulated lymphocyte blastic transformation occurred only in cultures of seropositive individuals, whereas none occurred in response to NDV. Delayed appearance of antiviral activity with the characteristics of IFN-gamma in HSV-stimulated PML cultures is a sensitive and specific measure of the human immune IFN response. Sequential synthesis of IFN-alpha and IFN-gamma in individual PML cultures provides an opportunity to examine regulation of IFN production in response to virus with intrinsic IFN-inducing properties. (Author abstract) (22 Refs)

22. IMMUNE (GAMMA) INTERFERON PRODUCED BY A HUMAN T-LYMPHOBLAST CELL LINE.

Nathan I, Groopman JE, Quan SG, Bersch N, Golde DW
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Nature (Lond); 292(5826):842-844 1981

The characterization of the interferon-gamma (IF-g) produced by a T-lymphocyte cell line (mo) derived from the spleen of a patient with hairy cell leukemia is reported. High IF-g levels were obtained in the presence of fetal calf serum, phytohemagglutinin (PHA), and 12-O-tetradecanoylphorbol-13-acetate; however, in serum-free medium, PHA induction alone gave max IF yield. The Mo IF was of the gamma type by the criteria of acid lability, stimulation of induction, production kinetics, and failure of neutralization by WBC IF antisera. Chromatographic analyses showed that IF-g was a hydrophobic glycoprotein with an apparent mol wt of 40,000. Physiochemically, Mo IF-g was distinct from the erythroid-potentiating activity, colony-stimulating activity, and neutrophil migration-inhibitory factor produced by Mo cells. This cell line should allow the large-scale production of IF-g for purification and clinical trials. (30 Refs)

23. TOTAL SYNTHESIS OF A HUMAN LEUKOCYTE INTERFERON GENE.

Edge MD, Greene AR, Heathcliffe GR, Meacock PA, Schuch W, Scanlon DB, Atkinson TC, Newton CR, Markham AF
ICI Pharmaceuticals Div., Mereside, Alderly Park, Macclesfield, Cheshire SK10 4TG, England
Nature (Lond); 292(5825):756-762 1981

A 514-base pair fragment of double-stranded DNA coding for human interferon-alpha1 (166 amino acid residues), and containing initiation and termination signals plus appropriate restriction enzyme sites for plasmid insertion, has been totally synthesized. The synthesis involved preparation of 66 oligodeoxyribonucleotides, ranging in size from 14 to 21 residues, plus 1 deoxydecanucleotide, by rapid, solid phase procedures, and enzymatic ligation of the oligonucleotides. After ligation of the synthetic gene to a plasmid vector and transformation of Escherichia coli, clones containing the anticipated gene sequence were obtained. (Author abstract) (55 Refs)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

24. TREATMENT BY LIMITED SURGERY AND SPECIFIC IMMUNIZATION OF GUINEA PIGS WITH STAGE II EXPERIMENTAL CANCER.

Hunter JT, Ashley MP, Sukumar S, Sugimoto T, Zbar B, Rapp HJ, Yarkoni E
Lab. Immunobiology, NCI, NIH, Bethesda, MD, 20205
J Exp Med; 154(2):253-261 1981

Line 10 (L10) cells were obtained from diethylnitrosamine-induced guinea pig hepatocellular carcinoma. Tumors were induced in male Sewall Wright strain 2 guinea pigs by id injection of 10(6) L10 cells in the flank. Tumors were allowed to progress to stage II with palpable tumor and first draining lymph node evident. The next draining lymph mode appeared normal but contained tumor cells. Treatment at stage II involved (1) limited surgery: excision of the tumor and primary lymph node; (2) extensive surgery: excision of the tumor, primary lymph node, and more distant lymph nodes; or (3) immunotherapy: 1 or 2 days after surgery and 6-7 days later a mixture of irradiated tumor cells and adjuvant BCG cell walls (BCG CW) was injected id. Each animal received 2 x 10(8) irradiated tumor cells and 750 ug BCG CW, with a second vaccine injection on the contralateral flank 7 days later. After 21 days all 12 animals treated by limited surgery showed metastases. Of these, 3 rejected a new tumor challenge. All 12 animals treated by extensive surgery were cured, of which 9 rejected a new tumor challenge. Immunotherapy after limited surgery was no more effective than extensive surgery. It did provide immunity to further tumor challenge. Two doses of immunotherapy were required. The method indicates possibilities for cancer therapy in humans. (15 Refs)

25. IMMUNOPOTENTIATING ACTIVITY OF WHOLE CELLS AND MINI-CELLS OF SALMONELLA TYPHIMURIUM.

Kurashige S, Yoshida T, Kodama K, Mitsuhashi S
College Medical Care and Technology, Gunma Univ., Showa-machi, Maebashi, Gunma 371, Japan
Microbiol Immunol; 25(5):467-477 1981

The effect of whole cells of an avirulent strain of Salmonella typhimurium and its mini-cells on humoral immunity, cellular immunity and phagocytosis of macrophages was studied in Balb/c, ICR, and DBA/2 mice. The iv inoculation with both whole cells and mini-cells produced stimulation of phagocytosis of mouse peritoneal macrophages; mini-cells were 1,000x less effective than whole cells. Both whole cells and mini-cells enhanced cell-mediated immunity against leukemia L1210 and sarcoma 180 cells. Whole cells stimulated the antibody-forming cells to produce IgG antibody of higher affinity. Mini-cells stimulated slightly blast cell transformation of lymphocytes from mesenteric lymph nodes of normal mice. (19 Refs)

MICROBIAL FRACTIONS AND EXTRACTS

26. BCG-CELL WALL IMMUNOTHERAPY OF PRIMARY CANINE MAMMARY CARCINOMA (MEETING ABSTRACT).

Harris SC, Winters WD, Lynd FT, Young RJ
University of Texas Health Science Center, San Antonio, TX, 78284
4th Annual San Antonio Breast Cancer Symposium, Nov 6-7, 1981, San Antonio, Texas Cancer Therapy and Research Center of South Texas; 1981

Under conditions which simulate human clinical trials to the max extent possible, pet dogs with spontaneously occurring breast cancers are being treated with pre-operative intralesional immunotherapy. Dogs with wedge biopsy proven mammary carcinomas are randomized to receive an intralesional injection of either BCG-cell walls (CW) or placebo (carrier alone) four wk prior to definitive surgery. At this time, none of the 28 BCG-CW treated dogs (0%) and 5 of the 24 placebo treated dogs (21%) have died of tumor. Eighteen of the BCG-CW treated dogs showed gross evidence of tumor regression prior to surgery. Histopathological examination of biopsy and surgical specimens showed an intense inflammatory response with significant destruction of adenocarcinomatous elements in the tumors injected with BCG-CW as compared to the placebo injected tumors. Classical primary antibody responses to BCG-CW were demonstrated by solid phase radiometric assay. Standard assays of cellular immunity (delayed cutaneous hypersensitivity, adherence inhibition, WBC migration inhibition and 51Cr release cytotoxicity techniques) were unable to distinguish between BCG-CW and placebo groups. However, BCG-CW was shown to stimulate long-lived increases in canine interferon. (no Refs)

27. REDUCED GENERATION OF PROCOAGULANT ACTIVITY BY ENDOTOXIN-STIMULATED MONONUCLEAR CELLS FROM PATIENTS WITH CHRONIC MYELOID LEUKAEMIA.

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Br J Haematol; 48(3):501-505 1981

The capacity of blood mononuclear cells to produce procoagulant activity upon stimulation with bacterial endotoxin in vitro was studied in 21 untreated patients with chronic myeloid leukemia (CML). Procoagulant activity developed by patients' cells after prolonged incubation with endotoxin was significantly lower than that produced by cells from a matched control group (p less than 0.001). Reduced activity was seen in all patients when each of them was compared to a matched control studied simultaneously. It was below 50% of the control in 19 patients, and in 8 of these it was less than 10%. These findings suggest that qualitative abnormalities in mononuclear cell function may exist in CML and might explain why these patients are less prone to thrombotic complications than those with other myeloproliferative diseases. (Author abstract) (22 Refs)

CYTOKINE THERAPY

28. SPONTANEOUS INTERLEUKIN 2(IL-2) PRODUCTION BY HUMAN LEUKEMIC CELLS IN TISSUE CULTURE (MEETING ABSTRACT).

Wernet P, Borowitz A, Ziegler A, Kramer PH, Pawelec G
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Immunobiol; 159(1/2):203 1981

Since IL-2 is conventionally from WBC activated with T cell mitogens, it was considered possible that pathologically active leukemic T cells might also be producing IL-2. Thus five established T cell lines as well as six clearly diagnosed T cell leukemias with different surface phenotypes - determined in indirect immunofluorescence with greater than 30 monoclonal antibodies - were screened fo r IL-2 production. These cells were cultured for short periods of time (6-72 hr) in RPMI 1640 medium containing 20% fetal calf serum and 10% human serum, and for some experiments supplemented with 1% phytohemagglutinin (PHA) or 10 ng/ml of the phorbol diester 12-O-tetradecanoyl-phorbol-13 acetate (TPA), or both. Only two out of five variants of JURKAT produced detectable amounts of IL-2, as measured in a standard thymidine incorporation microassay on cloned human and murine T cell lines; and two produced IL-2 without stimulation by mitogens. In addition, one of the active JURKAT variants was cloned by limiting dilution, and a clone derived which retained high spontaneous IL-2 production. Although exposure of active JURKAT lines to PHA or/and TPA produced a lymphokine superior to the uninduced IL-2 source in the 24 hr thymidine incorporation assay, suprisingly the reverse was observed when the IL-2 sources were compared for their actual ability to sustain long term growth of alloactivated cloned T cell lines for six days or longer. The two IL-2 producing JURKAT variants differed in three surface markers from the three non-IL-2 producing JURKAT variants. Of the six T cell leukemias two were found to produce IL-2 spontaneously as well as after PHA or/TPA induction. These two-both proliferating only slowly-were a Sezary cell type which produced only moderate amounts of IL-2 and a chronic lymphatic leukemia of T cell type which in contrast produced exceptionally high IL-2 activity, surpassing a conventionally prepared reference IL-2 source. (1 Ref)

29. THE GENERATION OF SPECIFIC CYTOTOXIC RESPONSES BY HUMAN LYMPHOCYTES REQUIRES ANTIGEN AND ACTIVITIES PROVIDED BY A LYMPHOKINE SUPERNATANT.

Warren HS
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Scand J Immunol; 14(1):71-76 1981

The requirements for the generation of specific cytotoxic responses by human lymphocytes have been investigated using as a model system the response to the UV light-killed mouse tumor P815. These requirements are antigen (P815UV) and activities provided by a human lymphokine (LK) supernatant. Cells that give rise to non-specific cytotoxicity can be separated on discontinuous Percoll density gradients after a 3-day incubation of peripheral blood leukocytes with the lymphokine supernatant, cells from which specific cytotoxic responses can subsequently be generated in the presence of P815UV and LK sediment at a higher density. (Author abstract) (18 Refs)

30. PRODUCTION OF AN ANTI-TUMOUR CYTOTOXIN BY HUMAN MONOCYTES.

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Immunology; 44(1):135-142 1981

Human monocytes incubated in vitro for 20 hr at 37 C release a factor which is cytotoxic to a number of human and murine tumor cell lines: untransformed cells appear to be less susceptible. A similar factor is produced under comparable conditions by myelomonocytic leukemic cells and by macrophages derived from monocytes by in vitro culture for 8 days. Max production of the factor occurred in the presence of fetal calf serum or autologous plasma and endotoxin. The factor is newly synthesized in culture as its production is reduced if the monocytes are treated with cycloheximide or actinomycin D or incubated at lower temperatures. Freshly isolated monocytes do not release the factor on freeze-thaw or hypotonic lysis. The monocyte cytotoxin has apparent mol wt of 34,000 on Ultrogel AcA54 gel filtration and 140,000 on gradient polyacrylamide gel electrophoresis; it has beta2-gamma1 electrophoretic mobility in polyacrylamide gel and does not appear to be C3a or arginase. (Author abstract) (18 Refs)

ACTIVE SPECIFIC IMMUNIZATION

31. GENERATION OF T CELL CYTOTOXICITY AGAINST SYNGENEIC LYMPHOMA CELLS BY ALLOIMMUNIZATION WITH NORMAL CELLS (MEETING ABSTRACT).

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Immunobiol; 159(1/2):192 1981

It has been reported that the in vitro stimulation of mouse or human lymphocytes to a pool of allogeneic normal cells could generate a significant cell-mediated cytotoxicity against syngeneic or autologous neoplastic cells. The aim of our experiments was to verify whether BALB/c (H-2d) mice immunized with allogeneic lymphoid cells either of single strains or of a pool of 6 different strains could develop antitumor activity to the BALB/c, Moloney-induced lymphoma YC8. Peritoneal exudate cells (PEC) were directly used as effectors 5 days after the last of 3-5 weekly immunization in a cell-mediated assay on YC8 cells, whereas spleen cells were restimulated in vitro with the same immunizing cells a mo after the last immunization, and then tested on YC8. Both PEC and spleen cells of BALB/c mice singly immunized to DBA/2 (H-2d) or B10.D2 (H-2d) lymphoid cells (but not to B10.M [H-2f], B10.A [H-2a] or BALB.B [H-2b]) or to a lesser extent to the pool of C3Hf (H-2k), DBA/2, NIH (H-2q), BALB,B B10.M, B10.A lymphoid cells, developed a significant cytotoxic activity on the syngeneic lymphoma YC8 without affecting control BALB/c blasts. These experiments also showed that in vitro killing of YC8 was restricted by gene products of the MHC, possibly of the Kd-IEd region. Competitive inhibition experiments showed that both YC8 cells and DBA/2 blasts, but not C3Ur11 (H-2k), Ur1 (H-2d) or LSTRA (H-2d) lymphomas inhibited the activity of BALB/c anti-DBA/2 effector cells on YC8 target. The cytotoxicity against the syngeneic tumor was mediated by T lymphocytes since it was abrogated by treatment with anti-Thy-1.2 serum plus complement. These data sugge st a cross-reaction between non-H-2 antigens of normal allogeneic lymphocytes DBA/2 or B10.D2 and antigens expressed by YC8. In vivo experiments showed that in addition to B10.D2 and DBA/2, the immunization of BALB/c mice with most but not all allogeneic lymphoid cells conferred resistance against the growth of YC8. The protection against YC8 growth elicited by B10.A but not by A (both having the same H-2a haplotype) alloimmunization of BALB/c mice confirmed that non-H-2d differences were of major importance in this phenomenon. (no Refs)

32. THE USE OF POLYMERISED AUTOLOGOUS TUMOR TISSUE PARTICLES FOR EXPERIMENTAL CANCER IMMUNOTHERAPY IN RATS BEARING SHAY CHLOROMA.

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Exp Pathol (Jena); 19(2):122-129 1981

The effects of the specific active cancer immunotherapy utilizing autologous tumor tissue particles polymerized with ethylchlorformiate, and used in combination with PPD tuberculin, were studied on the growth of chloroma in an inbred strain of Wistar rats. As control animals, rats not immunized, or immunized with autologous muscle tissue polymer + PPD, or PPD alone, were studied. A clear-cut enhancement of tumor growth was observed in the group of animals receiving the tumor polymer, as evidenced by the largest tumors, the lowest incidence of tumor rejection and the lack of histological signs of host response against the growing chloroma. Immunization with the PPD tuberculin, on the other hand, favorably influenced the host's immune system thus contributing to the tumor rejection and the development of pronounced host response in a high percentage of cases. The results were discussed in the light of favorable experiences gained with this mode of cancer immunotherapy in a number of clinical trials, as well as in a previous experimental DBA/2 mouse mastocytoma model. This apparent controversy between the previously obtained and the present results was interpreted to be caused by the different antigenic properties of the tumors used in these studies. The importance of the selection of an appropriate model system was emphasized in obtaining data relevant to human tumors from experimental cancer immunotherapy systems. (Author abstract) (40 Refs)

ADOPTIVE IMMUNIZATION AND RELATED APPROACHES

33. IN VITRO GROWTH OF MURINE T CELLS. VI. ACCELERATED SKIN GRAFT REJECTION CAUSED BY ADOPTIVELY TRANSFERRED CELLS EXPANDED IN T CELL GROWTH FACTOR.

Rosenstein M, Eberlein T, Kemeny MM, Sugarbaker PH, Rosenberg SA
Surgery Branch, NCI, NIH, Bethesda, MD, 20205
J Immunol; 127(2):566-571 1981

The ability of adoptively transferred cytotoxic T cells expanded in T cell growth factor (TCGF) to produce accelerated graft rejection of B10.BR skin grafts from normal B6AF1 recipient mice was tested. In vitro sensitized cells expanded in regular TCGF were capable of accelerating graft rejection when adoptively transferred iv 1 day after grafting. Cells expanded in LF-TCGF (lectin-free) were more effective in accelerating graft rejection than cells expanded in lectin containing TCGF. Nonsensitized cells or cells sensitized to irrelevant B10.D2 antigenic determinants in vitro and subsequently expanded in LF-TCGF were unable to induced accelerated rejection of the B10.BR grafts. Expanded cytotoxic effector cells known to be immunologically active in vivo were also unable to accelerate graft rejection if irradiated with 2,000 R before adoptive transfer. The ability of cells to lyse the appropriate targets in 4-hr 51Cr release assays correlated poorly with the effectiveness of these cells after in vivo injection. These studies are the first to demonstrate that cytotoxic cells expanded in TCGF are capable of mediating a cytotoxic function in vivo. (Author abstract) (18 Refs)

34. IN VIVO AND IN VITRO EFFECTS OF XENOGENEIC IMMUNE RIBONUCLEIC ACID IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA: A PHASE I STUDY.

Richie JP, Wang BS, Steele GD, Wilson RE, Mannick JA, Catalona WJ
Dept. Surgery/Urology, Peter Bent Brigham Hosp, Harvard Medical Sch., Boston, MA
J Urol; 126(1):24-28 1981

Based upon demonstration in our laboratory of repeated prevention of pulmonary metastases by adjuvant immune RNA in animal preparations, xenogeneic immune RNA was given in a phase I study to patients with advanced renal cell carcinoma. Six patients were treated with iv infusions of autologous lymphocytes incubated in vitro with immune RNA extracted from splenocytes of guinea pigs immunized with the patient's own tumor. Serial peripheral blood lymphocytes were obtained during and after each treatment with immune RNA for in vitro evaluation of cell-mediated cytolysis by 51Cr release assay and 125-I iododeoxyuridine assay against allogeneic renal cell carcinoma targets and melanoma targets. Neither toxicity nor enhancement of tumor growth was observed. All patients demonstrated significantly increased cell-mediated cytolysis against allogeneic renal cell carcinoma targets but no change against melanoma targets. Increased cell-mediated cytolysis could be demonstrated in individual blood samples after incubation with immune RNA. Further, progressive in vivo effect was demonstrated in in vitro assay of serial peripheral blood lymphocytes before each successive exposure to immune RNA. Increased cell-mediated cytolysis persisted in peripheral blood lymphocytes up to 9 mo after therapy. Although without controls one patient had complete response and two patients had partial responses (8 to 18 mo). Two patients had stabilization of the disease for 3 to 4 mo and one patient had progression of cerebral metastases. One patient is alive 24 mo after therapy. These results would favor the institution of a randomized prospective trial in patients with advanced renal cell carcinoma or lesser tumor burdens. (Author abstract) (25 Refs)

35. IN VIVO ANTI-TUMOR EFFECTS OF LOCAL ADOPTIVE TRANSFER OF MOUSE AND HUMAN CULTURED LYMPHOID CELLS.

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Int J Cancer; 28(2):157-164 1981

Mouse and human lymphoid cells were cultivated in the presence of T-cell growth factor (TCGF) and evaluated for their in vivo antitumor effect in mice. Cultured spleen cells of normal BALB/c mice or of mice bearing the M109 tumor had a high level of cytotoxic activity in vitro against a variety of tumor target cells and had characteristics of natural killer cells. These cultured cells were evaluated for their in vivo cytotoxic activity by admixture with [125I]dUrd-labeled M109 tumor cells (2 x 10(5)) at a 30:1 ratio and inoculation of the mixture into the footpads of BALB/c mice. The level of radioactivity remaining in the footpad was determined at various periods following inoculation of radiolabeled tumor cells. The presence of cultured cells in the inocula caused a marked decrease in the footpad radioactivity by 24 hr. However, the slope of clearance of the radiolabel then became similar to that in the control mice. The cultured cells delayed, but did not prevent, tumor appearance, and did not influence the subsequent rate of growth of the tumors. The transient effects of the cultured cells contrasted with the more prolonged in vivo effects of alloimmune lymphocytes, and this may be due to their short survival period. Ninety-nine percent of [125I]dUrd-labeled cultured mouse lymphoid cells were eliminated within 48 hr of i.f.p. inoculation. Cultured human lymphoid cells, initiated from the blood of normal donors, also had a high level of cytotoxic activity in vitro and were evaluated for their in vivo effects by intra-footpad inoculation into nude mice, together with radiolabeled human tumor cell lines, G-11 or HT-29. In vivo cytotoxic activity of the human cultured mouse and human effector cells have appreciable in vivo cytotoxic effects against tumor cell lines. However, the transient duration of these effects may limit their immunotherapeutic potential. (Author abstract) (18 Refs)

SEROTHERAPY AND RELATED APPROACHES

36. MODULATION OF LYMPHOCYTE ACTIVATION BY PLASMAPHERESIS IN ADVANCED MALIGNANT MELANOMA (MEETING ABSTRACT).

Salinas FA, Wee KH, Silver HK
No affiliation given
Immunobiol; 159(1/2):27 1981

These patients were subjected to serial plasmapheresis with pre- and post-treatment serum and lymphocytes evaluated by the following in vitro assays previously described by us: circulating immune complexes (CIC), anti-xenogeneic oncofetal antibody (anti-XOFA), total serum sialic acid (SA), and mixed lymphocyte reactivity (MLR). Each patient was followed for 4, 6, 7, 9, 12, 16 and 19 mo respectively. On one-way MLR stimulation with allogeneic cells, patient's lymphocytes tended to incorporate less thymidine than controls and this value remained depressed or further decreased after plasmapheresis for all 25 treatments in patients A, B, E, F, and G. The single evaluable pre and post MLR in patient C and the first MLR of patient D demonstrated increased thymidine incorporation following plasmapheresis. Conversely, autologous thymidine incorporation consistently increased in all patients, but not in patients C and D. Each plasmapheresis led to a measurable decrease in CIC, anti-XOFA and SA. CIC and anti-XOFA concentrations were independent and related to tumor burden as reflected by SA. A dynamic interaction of immune reactants was observed during 27 plasmapheresis treatments. Assuming that similar clearance rates for CIC, free antibody and unbound antigen were achieved upon plasmapheresis treatment, and that antigen concentration in these patients remained consistently in excess due to increased tumor burden, we observed that factors which reflected patient MLR capability included both pretreatment concentrations of CIC and free antibody. Patients A, C, D, E, and G reported symptomatic improvement following treatments in the absence of objective response in their advanced disease. In view of the relationship of tumor burden, CIC and anti-XOFA to effect of plasmapheresis on MLR, more timely treatment in patients with less extensive disease should be evaluated. (2 Refs)

37. IMMUNOTHERAPY OF MURINE LEUKEMIAS BY MONOCLONAL ANTIBODY. 1. EFFECT OF PASSIVELY ADMINISTERED ANTIBODY ON GROWTH OF TRANSPLANTED TUMOR CELLS.

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J Immunol; 127(2):805-810 1981

The objective of the present study was to establish a model system for the evaluation of passive immunotherapy of murine leukemias. Monoclonal antibodies directed at T lymphocyte differentiation antigens (Thy 1 and Lyt 2) were tested for their effect on tumors that were grown in hosts congenic for the target antigen. Tumor challenges were selected that were at least 500 x the dose that was lethal in 50% of untreated controls. The A strain leukemia, ASL.1, was transplanted sc into A/Thy 1.1 congenic hosts. Ip administration of anti-Thy 1.2 monoclonal antibodies of the IgG3 and IgM classes reduced tumor growth. Up to 90% of the mice receiving antibody of the IgG3 subclass failed to develop tumors, whereas IgM antibodies prolonged survival time, but the mice eventually died of tumors. Antibody was most effective if administered within 24 hr of tumor inoculation; delay of antibody injection for 48 hr prolonged host survival but did not eradicate cells at the injection site or prevent metastases. The C57BL/6-derived tumors, ERLD and EL4, were evaluated for susceptibility to treatment with antibody directed at the Lyt 2.2 alloantigen using the protocol that was effective in treating ASL.1. Monoclonal antibody of the IgG2a subclass was effective in the case of C57BL/6/Lyt 2.1 congenic mice bearing ERLD, but caused a decrease in survival time of mice bearing the transplanted EL4 tumor. Thus, antibody of the appropriate immunoglobulin subclass can be effective in controlling tumor growth if administered in the optimal treatment regimen, but inherent features of the tumor cell ultimately determine whether abrogation or enhancement of growth will occur. (Author abstract) (47 Refs)

38. IMMUNOTHERAPY OF MURINE LEUKEMIA. V. PROTECTION AGAINST FRIEND LEUKEMIA VIRUS-INDUCED IMMUNE COMPLEX GLOMERULONEPHRITIS BY PASSIVE SERUM THERAPY.

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JNCI; 67(3):703-717 1981

The development of immune complex glomerulonephritis in DBA/2 mice infected with Friend murine leukemia virus (F-MuLV) was compared with that in mice protected against virus-induced disease by administration of chimpanzee anti-F-MuLV antiserum (CaF-MuLV). Morphologic analysis of glomeruli from viremic (infected) normal chimpanzee serum-treated animals revealed significant renal disease within 2 wk following virus inoculation, with glomerular immune complex deposits and C-type viral particles seen by electron microscopy. Localization of F-MuLV envelope and core antigens (gp71 and p30, respectively) was also detected by immunofluorescence, as was murine IgG and C3. However, age-matched DBA/2 mice treated with CaF-MuLV antiserum alone or following F-MuLV inoculation showed no evidence of systemic disease and neither localization of F-MuLV antigens nor detectable virus particles. These data indicate that in addition to erythroleukemia, F-MuLV infection results in severe immune complex glomerulonephritis and that passive immunotherapy can protect susceptible mice from both aspects of viral pathogenesis. (Author abstract) (30 Refs)

39. INDUCTION OF IMMUNOLOGIC MEMORY IN MICE PROTECTED AGAINST FRIEND LEUKEMIA VIRUS-INDUCED DISEASE BY PASSIVE SERUM THERAPY (MEETING ABSTRACT).

Genovesi EV, Livnat D, Collins JJ
Department of Surgery, Duke University Medical Center, Durham, NC
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

DBA/2 mice, infected with Friend leukemia virus (FLV), are protected against progressive erythroleukemia by passive therapy with heterologous sera raised against disrupted virions or the purified major envelope glycoprotein, gp71, and develop a primary antibody response to FLV. The nature of the host anti-viral immune response generated during passive FLV-serum therapy was examined. FLV-infected mice treated with chimpanzee anti-FLV serum are protected for at least 190 days after primary infection and antibody to FLV persisted in the sera of these animals. Furthermore, serum protected mice challenged at various times after primary FLV infection rejected leukemogenic inocula of FLV and FLV-infected spleen cells, but did not reject FLC-745 cells, demonstrating acquired protective anti-viral immunity. Short-term prophylactic protection against FLV and FLV-infected spleen cells, but not to FLC-745 cells was observed when heterologous anti-FLV serum was administered before, rather than after the leukemia challenges. In view of the different kinetics of protection by serum prophylaxis when compared to serum therapy of FLV, it is clear that the resistance of FLV-serum protected mice to subsequent FLV challenge is not merely a function of prior serum treatment. The induction of host cellular resistance mechanisms is shown by the adoptive transfer of FLV-resistance by the spleen cells of FLV-serum protected mice but not by spleen cells from uninfected mice treated with the heterologous immune serum. (no Refs)

40. MONOCLONAL ANTIBODIES THAT DEMONSTRATE SPECIFICITY FOR SEVERAL TYPES OF HUMAN LUNG CANCER.

Cuttitta F, Rosen S, Gazdar AF, Minna JD
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Proc Natl Acad Sci USA; 78(7,part2):4591-4595 1981

Monoclonal antibodies with selectivity for human lung cancer were produced by immunizing BALB/c mice with an established line of human small cell lung cancer (NCI-H69) and fusing the mouse spleen cells to mouse myeloma line X63-Ag8.653. The resulting hybrid cells were initially screened by immunoautoradiography for production of antibodies that would react with NCI-H69 and another small cell lung cancer line (NCI-H128) but not its autologous B-lymphoblastoid line (NCI-H128BL). Stable monoclonal antibody-producing lines were isolated by repeated cloning. Three independently derived monoclonal antibodies, designated 525A5, 534F8, and 538F12, were found to react with three of the major types of human lung cancer (small cell, adenocarcinoma, and squamous carcinoma). They did not react with bronchioloalveolar and large cell lung cancers, myeloma, lymphomas, leukemias, osteogenic sarcoma, mesothelioma, hypernephroma, malignant melanoma, simian virus 40-transformed human fetal lung cells, skin fibroblast lines, human B-lymphoblastoid lines, human RBC, and rodent cells. Interestingly, these antibodies also bound to three out of three human neuroblastomas and two out of three breast cancers but failed to react with mouse neuroblastoma and rat pheochromocytoma. The monoclonal antibodies reacted with human small cell lung cancer tumors obtained at autopsy, but had insignificant reactions with normal human lung, liver, spleen, and skeletal muscle. We conclude that monoclonal antibodies have been generated that react with common antigenic determinants expressed on several human lung cancer types, neuroblastoma, and some breast cancers, but are not detectable by our current assays on a variety of other human tumors or normal adult human tissues. Such antibodies are of potential clinical and biological importance. (Author abstract) (50 Refs)

41. APPROACHES TOWARD IMMUNOTHERAPY OF 'NON-ANTIGENIC' TUMORS (MEETING ABSTRACT).

Ward EC, Bolognesil DP
Department of Biology and Immunology and Department of Surgery, Duke University Medical Center, Durham, NC
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 294 pp., 1981.

Our laboratory has been successful in the immunological management of several different tumors associated with type-C retroviruses by utilizing the virus antigens as targets for immune attack. There is a large body of virus negative tumors, however, which are non-antigenic and refractory to immunological manipulations. The current study deals with our initial attempts at rendering a virus negative methylcholanthrene-induced, transplantable sarcoma susceptible to immunotherapy after infection with FLV. Six courses of treatment with 0.5 ml of a high titered heterologous goat anti-FLV gp71 antiserum administered IP was found to have a profound effect on the outgrowth of the infected tumor (4% with tumor) when compared with normal goat serum (80% with tumor). The specificity of treatment was determined by conducting the therapy on the uninfected counterpart. In this case, there was no difference in tumor outgrowth between goat anti-gp71 treated, normal goat serum treated, or untreated groups. That the effect seen with the goat anti-gp71 is actual therapy is evident by the fact that successful treatment could be initiated at times when demonstrable tumor nodules were present. Thus, converting lowly antigenic virus negative tumors to highly antigenic virus positive tumors is a feasible approach toward rendering them susceptible to immunotherapy with anti-viral immune reagents. (no Refs)

OTHER BIOLOGICAL RESPONSE MODIFIERS

42. VITAMIN A-INDUCED MODULATION OF THE TRANSFORMED CELL PHENOTYPE IN VITRO.

Dion LD, Gifford GE
Lab. Viral Carcinogenesis, NCI, Bethesda, MD, 20205
Ann NY Acad Sci; 359:389-390 1981

The effects of Vitamin A (VA) on interferon synthesis, on the restoration of density-dependent inhibition of cell proliferation, and on other phenotypic markers of transformation in the

L-929 cell line are discussed. Experiments using HeLa cell spinner cultures to characterize the VA-induced inhibition of anchorage-independent growth are described. It was suggested that VA may play a role in maintaining normal growth controls although, perhaps, under very specific conditions. (3 Refs)

CLINICAL IMMUNOLOGY

43. NATURAL CYTOTOXICITY OF PERIPHERAL BLOOD LYMPHOCYTES AND REGIONAL LYMPH NODE CELLS IN BREAST CANCER IN WOMEN.

Cunningham-Rundles S, Filippa DA, Braun DW, Antonelli P, Ashikari H

Clinical Immunology and Tissue Typing Lab., Memorial Sloan-Kettering Cancer Center, 1274 York Ave., New York, NY, 10021

JNCI; 67(3):585-590 1981

Natural cytotoxicity was studied before surgery or other treatment in 83 women with primary, untreated breast cancer. Peripheral blood lymphocytes (PBL) and cytotoxicity of regional lymph node cell(s) (RLNC) were examined in a 4-hr 51Cr release assay against the target cell K-562. Results indicated that greater than one-third of breast cancer patients have more negative lymphocyte cytotoxic activity toward K-562 than do the other two-thirds. Similar results were observed for PBL of 25 patients found to have benign breast lesions. Of these patients, 23 had fibrocystic disease. The difference between these findings and findings with normal control lymphocytes studied in parallel was highly significant (p less than 0.001). The study of RLNC cytotoxicity in patients with breast cancer showed that 25% of the patients' RLNC had significant natural cytotoxic activity toward K-562. Incubation of RLNC with interferon in vitro before addition of labeled K-562 cells did not induce cytotoxicity in RLNC that did not have this activity initially. (Author abstract) (23 Refs)

44. ANTIBODY RESPONSE TO PNEUMOCOCCAL VACCINE IN PATIENTS WITH MULTIPLE MYELOMA.

Schmid GP, Smith RP, Baltch AL, Hall CA, Schiffman G

(c/o Baltch) Infectious Disease Section, Veterans Admin. Medical Center, Albany, NY, 12208

J Infect Dis; 143(4):590-597 1981

Patients with multiple myeloma and Waldenstrom's macroglobulinemia respond poorly to antigenic stimuli and may not be protected by pneumococcal vaccine. Thirty-seven patients and 10 controls received 14-valent pneumococcal capsular polysaccharide vaccine. The patients had lower (p less than 0.01) titers of antibody to 11 of the 12 antigens assayed before vaccination and to 10 of 12 antigens (p less than 0.01) after vaccination than did controls, but the ratios of antibody titers before vaccination to those after vaccination were remarkably similar. A poorer antibody response was observed in patients receiving multiagent chemotherapy than in those receiving chemotherapy with alkylating agents (p less than 0.01 for 6 of the antigens). That these patients did respond to the vaccine (although titers of antibody after vaccination were significantly lower than those in controls) suggests that patients with multiple myeloma or macroglobulinemia may benefit from pneumococcal vaccine. (Author abstract) (28 Refs)

45. MULTIVARIATE ANALYSIS OF T-CELL FUNCTIONAL DEFECTS AND CIRCULATING SERUM FACTORS IN HODGKIN'S DISEASE.

Schulof RS, Bockman RS, Garofalo JA, Cirrincione C, Cunningham-Rundles S, Fernandes G, Day NK, Pinsky CM, Iacefy GS, Thaler HT, Good RA, Gupta S

Dept. Medicine, Div. Hematology and Oncology, George Washington Univ. Sch. Medicine, 2150 Pennsylvania Ave., N.W., Washington, DC, 20037

Cancer; 48(4):964-973 1981

A comprehensive immunologic and serologic analysis was performed on 31 untreated patients with Hodgkin's disease. Immune evaluations stressed T-cell functional activity and included traditional parameters (PHA responsiveness and delayed hypersensitivity skin reactivity), as well as newer functional assays [T-cell colony formation, chemotaxis, spontaneous and antibody-dependent cytotoxicity, and concanavalin A-induced suppressor cell activity (CISA)]. Serum factors included ferritin, prostaglandins, zinc, copper, immune complexes, and thymic hormone activity. Every patient exhibited at least one T-cell or serum abnormality. The greatest percentage of patients exhibited T-cell defects in chemotaxis (85%), colony formation (81%), and PHA reactivity (64%). Immune defects were more common with advanced disease but were not related to absolute T-cell or monocyte count, skin test anergy, or abnormalities of Tmu/Tgamma cell proportions. Linear relationships were identified among abnormalities in the three assays employing mononuclear cells (PHA, colony formation, CISA) which may have reflected the inhibitory influence of monocytes present in the mononuclear cell preparations. Low serum zinc correlated with marked impairment of T-cell chemotaxis. Elevated prostaglandins were associated with high PHA reactivity and with depressed colony formation. Elevated prostaglandins were associated with high PHA reactivity and with depressed colony formation. Our results indicate that many complex factors, including intrinsic T-cell defects, contribute to the impaired immunity associated with Hodgkin's disease. (Author abstract) (62 Refs)

46. NATURAL ANTIBODIES TO THE HUMAN T CELL LYMPHOMA VIRUS IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA.

Posner LE, Robert-Guroff M, Kalyanaraman VS, Poiesz BJ, Ruscetti FW, Fossieck B, Bunn PA, Minna JD, Gallo RC

Lab. Tumor Cell Biology, NIH, Bethesda, MD, 20205

J Exp Med; 154(2):333-346 1981

Serum samples were obtained from patients with cutaneous T cell lymphoma (CTCL) and leukemia, and from 55 normal random donors. Retroviruses HTLV-CR (grown in HUT 102 cells) and HTLV-MB, isolated from patients CR and MB, respectively, were used, along with several other retroviruses. The sera were screened for the presence of natural antibody to HTLV-CR, using a solid-phase radioimmunoassay. Sera from patient CR and one other patient reacted specifically with proteins of HTLV-CR. CR serum also react ed with HTLV-MB proteins. Solid-phase immunocompetition and competition radioimmunoprecipitation assays demonstrated the specificity for HTLV-CR proteins. Patient CR antibodies were directed against viral core proteins with mol wt of 24,000 and 19,000, as shown by radioimmunoprecipitation analysis. Some reactivities to other animal retroviruses, including the baboon endogenous virus, simian sarcoma virus, feline leukemia virus, and gibbon ape leukemia virus, were demonstrated. These reactivities apparently were not virus-specific, but related to cellular antigen contamination of viral preparations or to antigens in fetal calf serum. The results indicate for the first time a specific antibody reaction to a retrovirus in humans. (38 Refs)

47. ANALYSIS OF T-LYMPHOCYTE SUBCLASSES IN LUNG CANCER (MEETING ABSTRACT).

Ginns L, Goldenheim P, Miller L, Hurwitz C, Burton R, Gillick L, Kazemi H
Pulmonary Unit and Transplantation Unit, Massachusetts General Hospital, Boston, MA
Am Rev Resp Dis; 123(4,Part2):58 1981

We analyzed peripheral blood lymphocytes (PBL) of 24 untreated lung cancer patients. We assayed subclasses of thymus-dependent (T)-lymphocytes by flow cytometry and indirect immunofluorescence with monoclonal anti-T-cell sera. We found alterations in total peripheral T-cells (OKT3+); inducer (helper) T-cells (OKT4+); and cytotoxic and suppressor T-cells (OKT8+). In lung cancer patients we found decreased percentage OKT3+ cells vs 8 non-smoking controls as well as vs 11 normal smokers. Subclasses of T-cells were normal. In primary squamous cell carcinoma, we found 24% reduction in percentage OKT3+ cells vs non-smokers. The percentage OKT3+ cells was not different from normal smokers. In metastatic lung disease we found 43% decrease in OKT3+ cells vs non-smokers, and 50% decrease in OKT4+ cells with normal percentage OKT8+ cells. In conclusion, we confirmed reports of decreased percentage T-cells in patients with lung cancer. In addition, we found that the pattern of immune defects in patients with primary squamous cell cancer was detectable in normal smokers: 1) reduced percentage PBL T-cells, 2) preserved absolute number T-cells, and 3) normal percentage of PBL in inducer and cytotoxic/suppressor T-cell subclasses. In patients with metastatic disease percentage T-cells and inducer subclass were reduced; the percentage suppressor/cytotoxic subclass remained normal and thus was a relatively greater proportion of T-lymphocytes. The similarity of immune defects in normal smokers and some cancer patients suggests that immune alterations due to smoking may antedate tumor growth. (no Refs)

48. C1Q BINDING ACTIVITY IN THE SERA OF PATIENTS WITH CHRONIC LUNG DISEASES.

Cooper KM, Moore M, Hilton AM
(c/o Moore) Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester 20, England
Clin Exp Immunol; 45(1):18-28 1981

Sera from patients with chronic lung diseases were tested for the presence of immune complexes (ICs) by the 125I-C1q-binding assay. Contrary to earlier reports, modification of the test system by addition of heparin decreased rather than increased the ability of the test to discriminate between control and pathological sera. Using the unmodified system, elevated C1q-binding activity (C1qBA) was found in patients with asthma (18%), chronic bronchitis (18%), sarcoidosis (18%), fibrosing alveolitis (50%), bronchogenic carcinoma (52%) and bronchiectasis (67%). Studies with the reducing agent 2-mercaptoethanol (2-ME) suggested a role for IgM rheumatoid factor (RF) and/or IgM-containing complexes in the C1q-reactive material of sera from patients with bronchiectasis and bronchogenic carcinoma. In the latter two groups, C1qBA was found to correlate with serum levels of IgG and IgA but not with C3 and C4. A weak correlation between levels of C-reactive protein (CRP) and C1qBA was found in the bronchogenic carcinoma group. Carcinoembryonic antigen (CEA) levels were elevated in all groups studied but no correlation with C1qBA was demonstrated, suggesting that CEA or CEA-ICs, if present, do not have an influence on the C1qBA of such sera. The results indicate that elevated serum C1qBA is a concomitant of both chronic inflammatory and neoplastic diseases of the lung but the extent of any similarity in the non-immunoglobulin components of the immune complexes in the respective conditions remains unknown. (Author abstract) (28 Refs)

49. POKEWEED MITOGEN-INDUCED GENERATION OF IMMUNOGLOBULIN-SECRETING CELLS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (MEETING ABSTRACT).

Rohl H, Enders B, Herrmann F, Teichmann H, Sieber G
Department of Haematology, Free University of Berlin, Berlin, W. Germany
Immunobiol; 159(1/2):130 1981

In the present study we have investigated the functional capacity of peripheral blood mononuclear cells from patients with chronic lymphocytic leukemia (CLL) to transform into immunoglobulin-secreting cells (ISC). After stimulation with Pokeweed mitogen (PWM) single ISC were enumerated in a reverse hemolytic plaque assay. Venous blood was taken from 41 patients with hematologically and histologically confirmed B-CLL. Lymphocytes from 36 patients who had markedly increased numbers of peripheral blood cells were found to be unable to generate ISC thus indicating that the leukemic B cells can not be activated. To exclude the possibility that the unresponsiveness was not due to a relative dilution of T helper cells, isolated B cells from the patients were cultured together with T cells from normal subjects. These experiments revealed that the unresponsiveness is indeed caused by an intrinsic defect of the leukemic cells. On the other hand, isolated T cells from CLL patients were found to be functionally normal helper cells when cocultured with normal B lymphocytes. However, only 5 patients who had all relatively low peripheral lymphocyte counts exhibited a significant response to PWM. Surprisingly, two of these patients had a severe antibody deficiency. In these two patients the effect of chemotherapy could be studied: the reduction of the peripheral lymphocytes resulted in a parallel and proportional increase in the number of ISC which was remarkably not followed by an increase in serum immunoglobulin levels. This finding suggests a normal B cell population present at least in some patients thus indicating that the immunodeficiency which is characteristic for CLL is not always due to an absence of functionally normal B lymphocytes but to cellular or humoral immunosuppressive mechanisms. (no Refs)

50. HISTIOCYTOSIS X - AN IMMUNE DEFICIENCY DISEASE? STUDIES ON ANTIBODY-DEPENDENT MONOCYTE-MEDIATED CYTOTOXICITY.

Kragballe K, Zachariae H, Herlin T, Jensen J
Dept. Dermatology, Marselisborg Hosp., DK-8000 Arhus C, Denmark
Br J Dermatol; 105(1):13-18 1981

Six children with histiocytosis X, all in clinical remission, were investigated for antibody-dependent cytotoxicity mediated by monocytes and neutrophils. Monocytes demonstrated a reduced cytoxicity and a normal Fc receptor activity. Judged by light microscopy the monocytes were normal. Preincubation with the patient's serum did not influence the cytotoxicity of normal monocytes. Neutrophils from patients with histiocytosis X showed a normal cytotoxic activity. We postulate a functional defect of the mononuclear phagocyte serum in histiocytosis X. (Author abstract) (19 Refs)

51. MEASUREMENTS OF CIRCULATING IMMUNE COMPLEXES IN CANCER PATIENTS (MEETING ABSTRACT).

Wilson RE, Rayner AA, Rodrick ML, Harte PJ, Munroe AE, Steele GD

Department of Surgery, Brigham and Women's Hospital, Boston, MA

Eur Surg Res; 13(1):32 1981

The presence of circulating immune complexes (CIC) has been demonstrated by numerous investigators using a variety of methods. We have modified the technique for aggregation of CIC by polyethylene glycol (PEG) which permits reproducible measurement by an increase in optical density and is not dependent on the class of immunoglobulin or the ability of the complexes to bind complement. Using this relatively simple test, we have critically analyzed the ability of this method to detect CIC using rabbit anti-BSA + BSA complexes. Soluble complexes were successfully detected in regions of antigen and antibody excess, and the results compared favorably with the classic Farr test for soluble complexes. We have compared the levels of CIC in normal human serum with those in the serum of patients with cancer and rheumatoid arthritis. In the cancer population, measurements have been made before and after surgical procedures - in patients with resectable or unresectable lesions - and in patients with or without sepsis. Patients with cancer had significantly higher PEG-CIC values than normals and lower values than rheumatoids. Patients with infection had significantly higher levels than normal while cancer patients with infection had significantly higher PEG-CIC levels than those with either cancer or infection alone. While mean preoperative values for patients with resectable and unresectable cancer were not different, PEG-CIC levels fell significantly in patients whose cancers were successfully resected. Patients with imcompletely resected malignancy showed no change in CIC levels in the postoperative sera. The possibility exists that levels of CIC in the serum can provide a record of biological events in cancer patients including tumor growth, response to treatment and cancer recurrence. (no Refs)

REVIEWS

52. ADJUVANT THERAPY WITH SURGERY: IMMUNOTHERAPY--OVERVIEW.

McGuire WP
Dept. Medicine, Section Medical Oncology, Univ. Illinois, Chicago, IL, 60612
Cancer Treat Res; 1:35-49 1981

The rationale for the use of biologic response modifiers (eg, BCG, Levamisole) in patients with bronchogenic cancer is discussed, and currently published and ongoing clinical trials of adjuvant immunotherapy are summarized. The trials include those in which BCG was used as an adjunct to chemotherapy (eg, cytoxan + adriamycin + vincristine) or radiotherapy in the case of small cell carcinoma. Trials of BCG and/or Levamisole as adjuncts to surgery in patients with non-small cell cancers also are reviewed. The failure of the trials to demonstrate the efficacy of immunotherapy over surgical treatment alone is noted, and suggestions are made for improving the design of future clinical studies. The past studies have been poorly designed with respect to adequate staging, proper balance for known prognostic factors, and patient numbers. In addition, the clinical trials have not included the concomitant, sequential studies of immune function that are necessary to determine the effects of the immunologic adjuvants on cellular immunity. (60 Refs)

53. ISOLATION OF IMMUNE COMPLEXES AND CHARACTERISATION OF THEIR CONSTITUENT ANTIGENS AND ANTIBODIES IN SOME HUMAN DISEASES: A REVIEW.

Jones VE, Orlans E
Postgraduate Medical Sch., Barrack Road, Exeter, Devon EX2 5DW, England
J Immunol Methods; 44(3):249-270 1981

Methods for the isolation and purification of immune complexes (ICs) from biological fluids in amounts sufficient for analysis are reviewed. Existing methods and new possibilities for the identification of constituent antigens and antibodies and of other serum components almost invariably found in ICs, such as complement and rheumatoid factors, are examined. Topics discussed include sample handling, contaminants in preparations of ICs, concentration of ICs, isolation of ICs (staphylococcal protein A, binding to receptors on Raji cell membranes, binding to complement components and conglutinin, binding to anti-immunoglobulins and anti-complement3, and binding to antigen-specific antibody), reagents for dissociation and elution of ICs, and detection of antigen and antibody. (107 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

CLINICAL TRIALS

1. TREATMENT OF DISSEMINATED MALIGNANT MELANOMA WITH HIGH-DOSE ORAL BCG.

Varella AD, Bandiera DC, De Amorim AR, Calvis LA, Santos IO, Escaleira N, Gentil F
Hospital A. C. Camargo Fundacao Antonio Prudente, Prudente, 211, 01509 Sao Paulo, SP, Brazil

Cancer; 48(6):1353-1362 1981

Thirty patients with unresectable disseminated melanoma (Stage IV) were treated with BCG (Moreau strain - Rio do Janeiro) by mouth, with weekly doses ranging between 200 mg and 28,000 mg. Five patients died in the first 2 mo of treatment. Of the remaining 25 patients, 2 (8%) showed complete regression, and 1 (4%) partial regression. Seven patients (28%) had stabilization of the disease for a 6-mo period, and 15 (60%) had progression of the disease. Complete and partial regressions were seen only in patients with extravisceral (sc) metastases, and were associated with a longer survival time. Regression of the sc metastatic nodules was always accompanied by the following local phenomena: increased temperature; local inflammation; softening, pain and pruritus at the nodule site; and a gradual decrease in size. At the site of the tumor mass, a hypochromic halo appeared. This halo remained permanently and was pathognomonic of the metastatic nodule rejection. When the halo was fully established, the inflammatory infiltrate was minimal and the malignant cells disappeared. If the area contained hairs, they underwent complete albinization. Serial biopsies of the nodules undergoing inflammatory changes and decreased consistency exhibited an intense cellular infiltration of lymphocytes, macrophages, and plasma cells around the malignant cells This sometimes simulated lymphoid follicle formation involving the melanoma cells associated with necrosis in a centripetal way. Some patients with visceral metastases (particularly pulmonary) had an unexpectedly long survival, apparently associated with interruption of the growth rate of the masses. Eleven out of 20 deaths were due to cerebral metastases. When cerebral disease was diagnosed, BCG was discontinued and the administration of corticoids was usually associated with a disappearance of the inflammatory signs at the nodule sites, but with progression of the disease. Toxicity was minimal. (Author abstract) (37 Refs)

2. CHEMOIMMUNOTHERAPY WITH LEVAMISOLE IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Pavlovsky S, Muriel FS, Garay G, Svarch E, Braier J, Lagarde M, Scaglione C, Eppinger-Helft M, Failace R, Dibar E
Instituto de Investigaciones Hematologicas, Pacheco de Melo 3081, 1425 Buenos Aires, Argentina

Cancer; 48(7):1500-1507 1981

Patients with acute lymphoblastic leukemia (ALL) who were in two consecutive protocols and in complete remission (CR) with maintenance therapy, were randomized to receive or not receive levamisole. A total of 15 of 55 low-risk patients of protocol 10-LLA-72 with levamisole had relapses, compared with 25 of 54 not receiving levamisole; 67 and 49%, respectively, remain in CR at 48 mo (p less than 0.025). In protocol 1-LLA-76, 14 of 91 low-risk patients on levamisole and 25 of 93 patients not receiving levamisole had relapses; 78 and 61%, respectively, remain in CR at 36 mo (p less than 0.05). Seventeen of 39 high-risk patients (children with a WBC count higher than 50,000 and adults) receiving levamisole had relapses compared with 37 of 61 not on levamisole. The DNCB skin test shows at 18 and 24 mo a 74 and 85% positivity in the levamisole group vs a 38 and 35% positivity in the control group (p less than 0.025). We conclude that levamisole prolongs the duration of CR and survival in low-risk patients with ALL. (Author abstract) (35 Refs)

3. IMMUNOSTIMULATION IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Konopka L, Ciesluk S, Zywicka-Lopaciuk H, Maslanka K, Sylwestrowicz T, Pawelski S, Karpowicz M
Instytut Hematologii, Chocimska 5, Warsaw, Poland

Przegl Lek; 38(5):437-441 1981

The effect of immunostimulation with levamisole (450 mg/wk for 6 wk or 150 mg/wk for 12 wk) on humoral and cellular immunity was studied in 25 patients with chronic lymphocytic leukemia. The patients were not receiving cytostatic and hormone treatment immunity (reduction of the IgA and IgM levels) was observed before levamisole treatment in all 25 patients. Improvement of the initially negative delayed hypersensitivity test was observed after levamisole treatment in 50% of the patients, and the DNA synthesis in lymphocytes was noted in 32%. The results confirm the beneficial immunoregulatory effect of levamisole in all patients. (15 Refs) (In POL)

4. THE RESULTS OF A COMBINATION INTERFERON AND SELECTIVE SURGERY IN THE TREATMENT OF OSTEOSARCOMA.

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Rev Chir Orthop; 67(3):193-197 1981

The treatment of 46 osteosarcoma patients with interferon (IF) (3 x 10(6) units/day, im, during hospital stay and 3 times/wk for 18 mo thereafter) and surgery is described. In 70% of the cases, the tumor was located near the knee. The diagnosis was confirmed in all 46 cases by biopsy. The results of this treatment is compared with those of patients treated between 1952 and 1971 and with those of patients treated with conventional methods (surgery and radiotherapy). The percentage of patients with metastases after 2 yr was 15% in the historical group, 30% in the conventional treatment group, and 50% in the IF/surgery group. At 5 yr, 27% of the conventionally treated patients were free of metastases while 50% of the IF/surgery patients showed no metastases. The 5-yr survival rates for the historical, conventional treatment, and IF/surgery groups were 15%, 30%, and 50%, respectively. Of the 46 patients treated with IF, 31 underwent amputation or disarticulation. In 15/46 cases, local resection of the tumor was possible. Of these 15 patients local recurrences necessitated amputations; 4/5 of these patients eventually died of pulmonary metastases. The results indicated that IF has some positive effect on the treatment of osteosarcomas. (14 Refs) (In FRE)

5. SEQUENTIAL COMBINATION CHEMOIMMUNOTHERAPY FOR VARIOUS MALIGNANT TUMORS: CLINICAL AND LABORATORY RESULTS.

Akiyoshi T, Kawaguchi M, Miyazaki S, Koba F, Tsuji H
Dept. Surgery, Res. Inst. Balneotherapeutics, Kyushu Univ., Beppu 874, Japan

Jpn J Surg; 11(4):283-290 1981

A new chemoimmunotherapy program was tested in 139 patients with various advanced malignant tumors. The program consisted of cyclophosphamide (200 mg, iv) on day 1, vibrio cholerae neuraminidase-treated autologous tumor cells admixed with BCG (id) on day 4, and mitomycin C (10-16 mg, iv) plus

5-fluorouracil (500 mg/iv) on day 7 of each course. Maintenance treatment with tegafur (600 mg, po) and immunostimulants was started on day 14. Ninety-nine patients were treated with one course of therapy followed by maintenance treatment for at least 6 mo; the remaining 40 patients received two to six courses at 1-to 6-mo intervals. Among the 65 evaluable patients, 14 (22%) had a favorable clinical response to the new regimen. Among patients with gastric carcinoma, survival was significantly longer in those receiving chemoimmunotherapy than in controls who received no adjuvant therapy. Cell-mediated immune response to autologous tumor extract was detected in 12/42 patients following therapy; immune reactivity measured by the PPD skin test and by phytohemagglutinin lymphocyte blastogenesis was slightly increased after treatment. Prognosis and post-therapy immune reactivity were significantly related, although there was no definite relationship between pretherapy skin reactivity and survival. The results suggest that immunocompetence may be essential to the effectiveness of this combination treatment. (14 Refs)

SYNTHETIC IMMUNOTHERAPEUTIC AGENTS

6. LEVAMISOLE AND SODIUM DIETHYLDITHIOCARBAMATE.

Renoux G
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Trends Pharmacol Sci; 2(9):248-249 1981

Problems in the relatively new field of immunopharmacology are illustrated by a review of experiences with the immunological enhancing agents levamisole (LV) and sodium diethyldithiocarbamate (DTC). Ideally, such agents should lack carcinogenicity or tumor enhancing effects, be devoid of antigenicity and sensitizing effects, exhibit known effects on various populations and subsets of immunocompetent cells, and be of known toxicity and pharmacological effects. Despite lack of information about the LV mode of action, need for active cancer therapy triggered a variety of clinical trials; many did not refer to available laboratory data or attempt to determine suitable dose, and only occasional studies accounted for immunological status of the patient. DTC has resulted from the translation of experimental data into clinical experience, making available a synthetic, chemically-defined compound devoid of undesirable cholinergic-like effects. Rodent studies indicate lack of carcinogenicity after daily feeding of DTC for 104-109 wk. DTC exerts a protective effect against some chemically-induced tumors and against ionizing radiation. At immunostimulant doses (0.5-25 mg/kg) the purified drug is essentially without toxicity or side effects. Modification of a patient's immune system is the ultimate hope of immunotherapy for treatment and even cure of cancer. (10 Refs)

7. MALEIC VINYL ETHER ACTIVATION OF MURINE MACROPHAGES AGAINST LUNG-METASTASIZING TUMORS.

Loveless SE, Munson AE
Dept. Immunology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
Cancer Res; 41(10):3901-3906 1981

A.M.W. 15,500 fraction of maleic vinyl ether (MVE-2) induced tumoristatic and tumoricidal activity in peritoneal macrophages of BALB/c and C57BL/6 mice following ip administration. Growth of B16 melanoma cells in vitro was inhibited up to 85% by MVE-2-activated, but not resident, peritoneal macrophages. In a tritiated thymidine release assay, B16 melanoma cells, and to a lesser extent Madison 109 lung carcinoma cells, were also sensitive to the cytolytic action of MVE-2-activated peritoneal macrophages. Administration iv of MVE-2 resulted in tumoristatic and tumoricidal activity in alveolar macrophages against radiolabeled B16 and Madison 109 lung carcinoma target cells. MVE-2-activated alveolar macrophages significantly inhibited L5178Y lymphoma colony formation following a 48-hr macrophage-tumor coincubation. BALB/c mice bearing the lung-metastasizing Madison 109 lung carcinoma footpad tumor were given MVE-2 iv, using the same dosing regimen that induced alveolar macrophages to be tumoricidal in vitro. Significant increase in life span were observed, suggesting that the antitumor activity of MVE-2 in this tumor system may be mediated by the activation of alveolar macrophages, with a resulting decrease in metastatic growth in the lung. (Author abstract) (30 Refs)

8. IMMUNOPOTENTIATION AND INHIBITION OF HERPES VIRUS ACTIVATION DURING THERAPY WITH LITHIUM CARBONATE.

Lieb J
41 Village Lane, Bethany, CT, 06525
Med Hypotheses; 7(7):885-890 1981

The successful treatment of nine patients (5 women, 4 men; aged 18-44 yr) with recurrent respiratory tract infections and other recurrent manifestations of defective immunity with lithium carbonate is reported. In addition, four patients (3 women, 1 man; aged 20-58) with recurrent herpes labialis treated with lithium also went into remission; in two patients, the effect appeared to be dose-dependent. (23 Refs)

9. THE IN SITU INDUCTION OF TUMORICIDAL ACTIVITY IN ALVEOLAR MACROPHAGES BY LIPOSOMES CONTAINING MURAMYL DIPEPTIDE IS A THYMUS-INDEPENDENT PROCESS.

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Cancer Metastasis and Treatment Lab., Frederick Cancer Res. Center, P. O. Box B, Frederick, MD, 21701
J Immunol; 127(4):1719-1720 1981

The ability of rat alveolar macrophage (AM) activation to occur in recipients that are unable to reject immunologically a syngeneic tumor was studied in three groups of mice. Group I, C3H/HeN mice were UV-irradiated for 8 wk. Group II mice, were nonspecifically immunosuppressed by thymectomy at 4 wk of age and by whole-body irradiation 1 wk later. Group III consisted of congenitally athymic NIH/S nude mice with well-characterized immune deficiency. In all experiments, mice were injected iv with multilamellar vesicles. AMs were injected iv. Macrophage-mediated cytotoxicity in vitro was measured by release of radioactivity from a 125I-iodo-deoxyuridine prelabeled B16 melanoma (syngeneic to C57BL mouse), UV-2237 fibrosarcoma (syngeneic to C3H/HeN mouse), or nontumorigenic fibroblast cell line (syngeneic to NIH/S mouse). AMs harvested from all groups of mice became tumoricidal in response to liposome-encapsulated muramyl dipeptide (MDP). Both the B16 melanoma and the UV-2237 fibrosarcoma cells were lysed by AMs harvested from the various recipients but the nontumorigenic fibroblasts were unharmed. The iv injections of liposomes containing Hanks' balanced salt soln and suspended in free MDP failed to render AMs tumoricida These results indicated that the liposome-entrapped MDP was responsible for the activation of AMs to become cytotoxic. (23 Refs)

10. INHIBITION OF LYMPH NODE METASTASIS OF P388 LEUKEMIA BY BESTATIN IN MICE.

Tsuruo T, Naganuma K, Iida H, Yamori T, Tsukagoshi S, Sakurai Y
Cancer Chemotherapy Center, Japanese Foundation for Cancer Res., Toshima-ku, Tokyo 170, Japan
J Antibiot (Tokyo); 34(9):1206-1209 1981

Bestatin, a chemically defined immunostimulant of low mol wt, suppressed the gradually-occurring lymph node metastasis of P388 leukemia in CDF1 mice when administered ip at the doses of 1 and approx 30 ug/mouse. It could not, however, suppress the established large metastasis of P388 leukemia. Lymph node cells isolated from the mice given bestatin ip at 1 and 30 ug/mouse showed stronger cytostatic activity against P388 leukemic cells in vitro than those from the untreated mice. (Author abstract) (10 Refs)

INTERFERON

11. THE EFFECT OF HUMAN FIBROBLAST INTERFERON (HUIFN-BETA) ON MALIGNANT TUMORS; IN VITRO EXPERIMENTS (MEETING ABSTRACT).

Arai T, Nagai M, Kasage S, Yasuda S
Dept. Neurosurgery, Dokkyo Univ. Sch. Medicine, Mibu-machi, Tochigi Prefecture 321-02, Japan
Program and Abstracts of the 22nd Workshop on Selected Topics of the Japanese Society of Neuropathology held in Fukuoka, Japan, 9-11 May, 1981. The Japanese Society of Neuropathology, Kyoto 602, Japan, 136 pp., 1981.

Cultured brain tumor tissues obtained at the time of surgery were treated with HuIFN-beta or lymphocytes. A culture of a medulloblastoma obtained from a 6-yr-old boy was treated, beginning in 1 wk, with 0.7 x 10(1) IU or 0.7 x 10(3) IU of HuIFN-beta per ml three times a wk for 2 wk, and the growth rate was compared with that of the controls. The growth of the tissue in the petri dish containing 0.7 x 10(3) IU of HuIFN-beta per ml was inhibited 86%, as measured by colony area, as compared with the control, which agreed with the clinical effect on this patient. Morphological changes were seen in the cells given 7 x 10(3) IU of HuIFN-beta per ml; the cells generally became long and thin and some had a differentiated astrocyte-like appearance with long projections. The growth of the glioma cell line was not inhibited by the addition of 0.7 x 10(3) IU of HuIFN-beta per ml. The growth of malignant astrocytoma tissue from a 29-yr-old male patient was inhibited by 12%, 65%, and 85% compared to the control when the autochthonous peripheral lymphocytes alone, HuIFN-beta (3 x 10(3) IU/ml) alone, and lymphotes + HuIFN-beta, respectively, were added. The 51Cr release assay using K562 cells as the target cells showed cytotoxicity of 4.7% for HuIFN-beta alone and 40% for the HuIFM-beta + lymphocytes. Cytotoxicity was about 30% when the lymphocytes were incubated with HuIFN-beta for 2 hr, washed and then applied to the target cells. These results indicate that HuIFN-beta has a direct effect on the tumor and an effect mediated by lymphocytes, the greatest tumor growth inhibition or cytocidal effect being produced when HuIFN-beta and the lymphocytes were added together. (no Refs) (In JPN)

12. INHIBITORY EFFECTS OF HUMAN LEUKOCYTE AND FIBROBLAST INTERFERONS ON NORMAL AND CHRONIC MYELOGENOUS LEUKEMIC GRANULOCYTIC PROGENITOR CELLS.

Williams CK, Svet-Moldavskaya I, Vilcek J, Ohnuma T, Holland JF
Dept. Neoplastic Diseases, Mt. Sinai Sch. Medicine, One Gustave Levy Place, New York, NY, 10029
Oncology; 38(6):356-360 1981

Inhibitory effects of two human interferon preparations, WBC interferon (Le-IF) and fibroblast interferon (F-IF), on granulocytic progenitor cells (CFU-C) from hematologically normal cancer patients and from patients with chronic myelogenous leukemia were evaluated. There was a wide variation in sensitivity of CFU-C to both Le-IF and F-IF. F-IF was more inhibitory against CFU-C than Le-IF. Normal CFU-C and chronic myelogenous Leukemia CFU-C were equally inhibited by both interferons. Effects of both interferons were neutralized by corresponding specific antisera but not by the other antisera. These observations confirmed that differences in immunogenicity of the interferons may attend their different origins. (Author abstract) (22 Refs)

13. HUMAN LARGE GRANULAR LYMPHOCYTES: SPONTANEOUS AND INTERFERON-BOOSTED NK ACTIVITY AGAINST ADHERENT AND NONADHERENT TUMOR CELL LINES.

de Landazuri MO, Lopez-Botet M, Timonen T, Ortaldo JR, Herberman RB
Dept. Immunology, Clinica Puerta de Hierro Universidad Autonoma, Madrid, Spain
J Immunol; 127(4):1380-1383 1981

Human natural killer (NK) cells against K-562 tumor cells have been morphologica lly identified as large granular lymphocytes (LGL). We have investigated whether LGL are also responsible for NK activity against a variety of adherent and nonadherent tumor cell lines. LGL-enriched fractions, obtained by centrifugation of nonadherent mononuclear cells on discontinuous density gradients of Percoll, contained high levels of spontaneous and interferon-(IFN) boosted NK activity against each the target cells tested. In contrast, the LGL-depleted fractions, which contain most of the typical small lymphocytes, were devoid of NK activity and did not develop appreciable activity after treatment with IFN. The ability of the different fractions to exert NK activity correlated with their capacity to form conjugates with nonadherent tumor cells. Reconstitution of the different fractions with macrophages did not increase the NK activity of already cytotoxic fractions and did not induce appreciable activity in the LGL-depleted fractions. On the other hand, mixtures of highly cytotoxic and nonreactive cell fractions did not reveal the presence of suppressor cells for NK in the nonreactive fractions. Taken together, our data demonstrate that both spontaneous and IFN-boosted NK activity is confined to the LGL-enriched fractions and suggest that LGL are the main effector cells exerting NK cytotoxicity against a variety of adherent as well as nonadherent tumor cell lines. (Author abstract) (17 Refs)

14. THE DUAL INTERACTION OF PROSTAGLANDIN E2 (PGE2) AND INTERFERON (IFN) ON NK LYTIC ACTIVATION: ENHANCED CAPACITY OF EFFECTOR-TARGET LYTIC INTERACTIONS (RECYCLING) AND BLOCKAGE OF PRE-NK CELL RECRUITMENT.

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Dept. Medicine, Div. Gastroenterology, Univ. California Los Angeles Center for Health Sciences, Los Angeles, CA, 90024
J Immunol; 127(4):1424-1428 1981

In this study we addressed the question of whether the known NK activators prostaglandin E2 (PGE2) and interferon (IFN) can synergistically activate NK lysis and whether they potentiate the same or different subsets of NK cells. We demonstrated that the activation of NK lysis can be enhanced as well as blocked by the interaction of these two activators. The enhancement of activation was not due to recruitment of separate subsets of pre-NK cells, but rather the synergistic enhancement of the recycling capabilities of the same set of NK cells. There was a temporal relationship to this enhancement. That is, if PGE2 was added during cellular processing required for full expression of NK activation induced by IFN, pre-NK lytic potential was inhibited. If, on the other hand, PGE2 is added after completion of full expression of the IFN-induced activated lytic process, there is enhancement of recycling capabilities of the same number of NK cells. (Author abstract) (18 Refs)

15. INTERFERON ENHANCES THE ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC) OF HUMAN POLYMORPHONUCLEAR LEUKOCYTES.

Hokland P, Berg K
Med. afd. II, Aarhus Amtssygehus, 8000 Aarhus C, Denmark
J Immunol; 127(4):1585-1588 1981

Polymorphonuclear WBC (PMN) from healthy volunteers were tested for ADCC activity against both RBC and tumor targets with and without the addition of human WBC interferon (IFN). It was demonstrated that IFN within 30 to 60 min enhanced the reaction in a dose-dependent manner with minimal IFN doses ranging from 1 to 100 units. Formal proof that the augmenting agent was IFN was obtained by using pure IFN proteins in combination with both mock-IFN preparations, which showed no enhancing activity, and anti-IFN antisera, which inhibited the action of the completely purified IFN protein. In the light of data demonstrating that the IFN effect was most pronounced when the IgG antibodies in the ADCC reaction were present in suboptimal amounts, it is hypothesized that IFN may play a special role in the early nonspecific immune response against non-self antigens. (Author abstract) (14 Refs)

16. MECHANISM OF STIMULATION OF NATURAL KILLER-CELL CYTOTOXICITY BY INTERFERON AND AN INTERFERON-INDUCER IN THE RAT.

Flexman JP, Shellam GR
Dept. Microbiology, Univ. Western Australia, Queen Elizabeth II Medical Centre, Nedlands, Western Australia 6009, Australia
Immunology; 44(2):311-320 1981

The interferon-inducer Newcastle disease virus (NDV) was shown to augment cytotoxicity attributable to natural killer (NK) cells in all of the major lymphoid organs of W/Fu rats except the thymus. The levels of interferon isolated from the spleen following NDV inoculation correlated with the increase in splenic cytotoxicity from the same spleen. Spleen-derived interferon was shown to augment splenic cytotoxicity following iv inoculation, and to augment spleen cell cytotoxicity in vitro. Three major peaks of interferon Type I were found in spleen homogenates corresponding to mol wt of greater than 100,000, 29-33,000 and 19-23,000. All these fractions stimulated spleen cell cytotoxicity when tested in vitro. The rapid drop in splenic cytotoxicity 24 hr after NDV inoculation was associated with a rapid fall in interferon levels in vivo. The need for the continued presence of interferon for the stimulation of cytotoxicity was demonstrated when spleen cells pretreated with interferon for 4 hr in vitro lost their augmented cytotoxicity upon culturing for a further 20 hr in the absence of interferon. Although splenic cytotoxicity returned to control levels within 24 hr of a single 107.3 EID50 dose of NDV, repeated doses of NDV maintained augmented cytotoxicity over a longer period. Spleen cells either taken from rats injected with NDV or pretreated in vitro with interferon showed a two-fold increase in the number of cytotoxic cells bound to W/FuG-1 target cells, with no change in the target binding-cell numbers. However, only the cell s pretreated with interferon showed an increase in lytic efficiency. (Author abstract) (30 Refs)

17. ASSOCIATION OF PHENOTYPIC REVERSION OF TRANSFORMED CELLS INDUCED BY INTERFERON WITH MORPHOLOGICAL AND BIOCHEMICAL CHANGES IN THE CYTOSKELETON.

Brouty-Boye D, Cheng YS, Chen LB
Lab. Viral Oncology, Institut de Recherches Scientifiques sur le Cancer, BP 8, 94802 Villejuif Cedex, France
Cancer Res; 41(10):4174-4184 1981

The distribution of microfilament bundles, intermediate filaments, microtubules, vinculin plaques, and extracellular fibronectin matrices was examined by indirect immunofluorescence in x-ray-transformed C3H/10T1/2 cells. The transformed phenotype correlated with a lack of actin cables and vinculin-containing plaques. Both interferon-treated and untreated transformed cells displayed a similar distribution of mitochondria, intermediate filaments, microtubules, and fibronectin. Significant qualitative and quantitative differences between the two types of cells were found in the proteins associated with the cytoskeletal framework by two-dimensional gel analysis. (Author abstract) (27 Refs)

18. INTERFERON INDUCES PERIPHERAL LYMPHADENOPATHY IN MICE.

Gresser I, Guy-Grand D, Maury C, Maunoury MT
Lab. Viral Oncology, Institut de Recherches Scientifiques sur le Cancer, BP 8, 94802 Villejuif Cedex, France
J Immunol; 127(4):1569-1575 1981

Inoculation (ip or iv) of partially purified or highly purified (HP) mouse interferon (electrophoretically pure in SDS-PAGE gels) into different strains of mice (C3H, BALB/c, Swiss, heterozygote and athymic nu/nu C57BL/6) results in a marked increase in the wt and in the total number of cells in axillary and inguinal lymph nodes. Interferon injected into the hind footpad induced an increase in the wt of the ipsilateral popliteal lymph node compared with the contralateral lymph node. Inoculation of noninterferon proteins (impurities) obtained in the course of purification of this HP interferon, mock interferon, or human WBC interferon were without effect. Experiments were undertaken to elucidate the mechanism by which interferon induced an increase in the wt (number of cells) of peripheral lymph nodes. There was no evidence that the afflux of transferred chromium-labeled lymphoid cells to lymphoid tissue was increased in interferon-treated recipient mice. There was no evidence that interferon treatment resulted in a stimulation of the multiplication of cells within the peripheral lymph nodes. Since we observed a decrease in the number of lymphocytes in the thoracic duct lymph and in the peripheral blood of interferon-treated mice, we suggest that interferon treatment resulted in an inhibition of egress of lymphocytes from lymphoid tissue. The finding that interferon treatment of mice alters patterns of lymphocyte circulation may be relevant to some of the effects of interferon on the immune system and may explain in part the lymphadenopathy observed in the course of some viral infections. (Author abstract) (51 Refs)

19. INTERFERONS, DOUBLE-STRANDED RNA, AND RNA DEGRADATION. ISOLATION AND CHARACTERIZATION OF HOMOGENEOUS HUMAN (2'-5')(A)N SYNTHETASE.

Yang K, Samanta H, Dougherty J, Jayaram B, Broeze R, Lengyel P
Dept. Molecular Biophysics and Biochemistry, Yale Univ., New Haven, CT, 06511
J Biol Chem; 256(17):9324-9328 1981

One of the mediators of interferon action is (2'-5')(A)n synthetase. If activated by double-stranded RNA it converts ATP into pyrophosphate and (2'-5')(A)n. In turn, (2'-5')(A)n activates a latent endoribonuclease (RNase L) which cleaves single-stranded RNA. We report here the isolation and characterization of a homogeneous human (2'-5')(A)n synthetase. The enzyme was purified from interferon-treated HeLa S3 cells by chromatography of a ribosomal salt wash fraction on DEAE-cellulose, poly(I).poly(C) agarose, and CM-cellulose. The purified (2'-5')(A)n synthetase can convert over 90% of ATP into (2'-5')(A)n. The enzyme is unstable but can be stabilized by certain nonionic detergents (eg Triton X-100). Its apparent Mr = 100,000, as determined by gel electrophoresis in sodium dodecyl sulfate, and about 80,000, as determined by centrifugation through a glycerol gradient. The human (2'-5')(A)n synthetase is similar to the corresponding enzyme from mouse Ehrlich ascites tumor cells, but differs from the latter size (100,000 vs 105,000 daltons) and in ionic conditions required for max activity. (Author abstract) (33 Refs)

20. PURIFICATION AND CHARACTERIZATION OF RECOMBINANT HUMAN LEUKOCYTE INTERFERON (IFLRA) WITH MONOCLONAL ANTIBODIES.

Staehelin T, Hobbs DS, Kung H, Lai CY, Pestka S
Pharma Res. Div., F. Hoffmann-La Roche and Company, Ltd., CH-4002, Basel, Switzerland
J Biol Chem; 256(18):9750-9754 1981

Recombinant human WBC interferon produced in bacteria (IFLrA) was purified to homogeneity with the use of monoclonal antibodies against WBC interferon. The purified interferon exhibited a single band of Mr = approx 19,000 on sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Amino acid analysis and the NH2-terminal sequence were consistent with the sequence predicted from the DNA. Some of the purified product contained NH2-terminal methionine; the terminal methionine was removed from the rest of the chains. (Author abstract) (18 Refs)

21. ANTITUMOR AND RADIATION SENSITIZING EFFECTS OF HUMAN LEUKOCYTE INTERFERON IN VITRO.

Ito H
Dept. Radiology, Kyoto Prefectural Univ. Medicine, Kyoto, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(6):551-558 1981

The antitumor and radiation sensitizing effects of interferon (IF) on human fibroblasts and KB cells were studied in vitro. Both types of the cells were irradiated by 60Co-gamma-rays. When the fibroblast was cultured with IF preparation, IF preparation did not suppress its growth; but the growth of the KB cell was suppressed by IF treatment. When the fibroblast was irradiated together with IF treatment (pretreated and posttreated), no effect was detected on its growth. When the KB cell was irradiated together with IF preparation, only posttreatment with IF preparation affected its growth. Furthermore, the KB cell was studied by the colony formation method. The radiation effect was enhanced by treatment with IF preparation. (Author abstract) (18 Refs) (In JPN)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

22. ANTITUMOR ACTIVITY OF TWO BCG VACCINE PREPARATIONS AGAINST THE LEWIS LUNG CARCINOMA IN MICE.

Lagrange PH, Gheorghiu M
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Cancer Immunol Immunother; 11(3):217-224 1981

Two BCG vaccines were prepared: Immuno-BCG Pasteur F (IPF) from surface culture and BCG-RIV (RIV) from homogeneously stirred deep cell culture. Pathogen-free inbred C57BL/6 female mice were injected with cells from Lewis lung carcinoma (3LL) malignant metastasizing tumor. The effects of sc injections of IPF or RIV at various times and concentrations on delayed local reaction (DLR), delayed-type hypersensitivity (DTH), and the number of viable BCG in draining lymph nodes were studied. Injection of IPF (7.6 x 10(6) viable units) or RIV (7.5 x 10(6) viable units) 14 days before injection of the tumor cells had no effect on the development of tumors or mean survival time. Injection of IPF or RIV simultaneously with tumor cells at the same site produced a slight delay in tumor growth. IPF produced a greater and more prolonged DLR than RIV when injected with the tumor cells. IPF induced a greater DTH antitumor reaction in BCG-immunized mice than RIV, but the DTH was greater with either BCG vaccine when mice were preimmunized with RIV than when they were preimmunized with IPF. Hence the vaccines differed; their ability to induce DLR was inversely related to their ability to induce DTH. The results suggest that BCG vaccines should be evaluated by their dry wt, rather than by number of viable units. If BCG therapy is to be used in tumor patients, it is important to determine a patient's sensitivity to mycobacterial antigens. (14 Refs)

23. MECHANISMS OF ANTI-TUMOR ACTION OF CORYNEBACTERIUM PARVUM. I. POTENTIATED TUMOR-SPECIFIC IMMUNITY AND ITS THERAPEUTIC LIMITATIONS.

Dye ES, North RJ, Mills CD
Trudeau Inst., Inc., Saranac Lake, NY, 12983
J Exp Med; 154(3):609-620 1981

A model currently being used to analyze the potential and limitations of tumor immunotherapy with Corynebacterium parvum is described. It was shown that implanting of the hind fo otpad of mice with 2 x 10(6) P815 mouse mastocytoma or methylcholanthrene (Meth A)-induced tumor (Meth A fibrosarcoma) cells admixed with 100 ug C parvum resulted in the emergence of a tumor that grew for a period of 9-10 days and then regressed. Regression of the C parvum-treated tumor failed to occur in mice that were gamma-irradiated, or made T cell deficient by thymectomy and lethal irradiation, and restored with bone marrow cells. These results, together with the finding that the onset of C parvum-induced tumor regression was associated with the generation in the spleen and draining node of T cells that were capable of adoptively immunizing normal mice against growth of a tumor implant, was consistent with the hypothesis that the therapeutic effect of C parvum is based on its capacity to potentiate the generation of T cell-mediated antitumor immunity. It was also shown that the mechanism responsible for this regression was capable of causing the regression of an untreated test tumor growing at a distant site, and that this therapeutic action was based on a T cell-mediated immune response to tumor-specific transplantation antigens. The immunotherapeutic action of the C parvum-tumor cell admixtures against a distant test tumor was limited to a test tumor below a certain critical size. (23 Refs)

24. MECHANISMS OF ANTI-TUMOR ACTION OF CORYNEBACTERIUM PARVUM. II. POTENTIATED CYTOLYTIC T CELL RESPONSE AND ITS TUMOR-INDUCED SUPPRESSION.

Mills CD, North RJ, Dye ES
Trudeau Inst., Inc., Saranac Lake, NY, 12983
J Exp Med; 154(3):621-630 1981

The capacity of an admixture of Corynebacterium parvum and P815 mastocytoma tumor cells implanted into B6D2 F1 mice to cause the rejection of a small test tumor growing at a distant site was studied in relation to the augmented production of cytolytic T cells in the lymph node draining the site of injection of the therapeutic admixture. A companion paper showed that implanting P815 tumor cells admixed with C parvum resulted in the emergence of a tumor that grew progressively for 9-10 days and then regressed. In addition, it was shown that the onset of tumor regression was preceded by a substantial generation in the draining lymph node and spleen of T cells capable of specifically lysing P815 target cells in vitro. Because the production of cytolytic T cells was much greater in response to the tumor growing in the presence of C parvum than in response to a tumor growing alone, it was suggested that the therapeutic action of C parvum when admixed with the tumor cells is based on its capacity to potentiate the production of cytolytic T cells. The adjuvant action was revealed by the additional finding that gamma-irradiated tumor cells failed to evoke the generation of T cells unless they were injected admixed with C parvum. Additional related study in DBA/2 mice showed generation of less peak cytolytic activity than B6D2 mice in response to C parvum and P815 cells; the tumors in DBA/2 mice did not completely regress. (13 Refs)

25. ADRIAMYCIN-ACTIVATED MACROPHAGES AS TUMOR GROWTH INHIBITORS.

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Cancer Res; 41(10):3852-3856 1981

Flow cytometry has been used to study the influence of Adriamycin- and Corynebacterium parvum-elicited cytostatic macrophages on the cell cycle of HeLa cells. Macrophages harvested from the peritoneal cavity of mice given ip injections of Adriamycin retain cytostatic activity for 3 to 4 days in vivo. Many of these macrophages fluoresced with the red emission spectra characteristic of Adriamycin. The decline in the presence of macrophages exhibiting red fluorescent cytoplasmic particles paralleled the loss in cytostatic activity. Drug-induced cytostatic macrophages exhibited at least as high a level of growth inhibition as did C. parvum-activated cells. In contrast to the apparent G1 block of HeLa cells which resulted from interaction with C. parvum-activated macrophages, Adriamycin-stimulated macrophages inhibited growth in the G2-M phase characteristic of the free drug. Multiple freeze-thaw cycles removed all activity from C. parvum macrophages but had no influence on the adriamycin-elicited effector cell activity. The data suggest that in vivo drug storage by macrophages may represent an important step in tumor cell destruction by Adriamycin. (Author abstract) (16 Refs)

MICROBIAL FRACTIONS AND EXTRACTS

26. COMPARISON OF ANTITUMOR EFFECT OF TWO DISTINCT IMMUNOPOTENTIATING AGENTS ON A SYNGENEIC SOLID TUMOR TRANSPLANTED TO NU/NU OR NU/+ MICE.

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Nippon Ganka Gakkai Zasshi; 82(4):324-336 1981

The antitumor effect of two immunopotentiating agents, OK-432, a streptococcal preparation, and levamisole was compared in several aspects. A fibrosarcoma, KKN-1, which was induced in a BALB/c mouse by 3-methylcholanthrene and had been maintained by serial transplantations in BALB/c nu/+ or nu/nu mice, was used as a tumor, and syngeneic nu/nu or nu/+ mice were used as tumor hosts. OK-432 at a daily dose of 50 KE/kg or levamisole at a daily dose of 1 mg/kg was administered ip to mice. Neither drug showed any effect on the growth of KKN-1 transplanted to nu/nu mice, whereas both drugs inhibited the tumor growth in nu/+ mice. These results indicate the importance of T cell function of the mice in the antitumor effect of both drugs. This was also suggested by the results that impaired blastogenic response to phytohemagglutinin or concanavalin A of spleen cells from tumor-bearing nu/+ mice significantly recovered by treatment of the mice with either drug. Winn's tumor neutralizing assay also showed antitumor activity of spleen cells of tumor-bearing nu/+ mice treated with OK-432. Administration of either drug daily from 1 day to 5 days after tumor transplantation showed pronounced antitumor effect, whereas the same dose given from 6 to 10 days after the transplantation showed reduced effect. OK-432, but not levamisole was effective even when the drug was given daily for 5 days before the tumor transplantation. Combined immunochemotherapy using OK-432 and mitomycin

C (MMC) showed a synergistic effect when OK-432 was administered after MMC, while no additive effect was obtained when the sequence of the administration of the two drugs was reversed. Additive effect was observed when levamisole was combined with MMC, regardless of the sequence of the administration. (47 Refs) (In JPN)

27. AUGMENTATION OF ADCC IN MICE BY MICROBIAL FRACTIONS.

Richman SP, Chism VT, Murphy SG
Cancer Center, 129 East Broadway, Louisville, KY, 40292
Cancer Immunol Immunother; 11(3):233-238 1981

The effects of a multicomponent microbial vaccine on murine splenocyte antibody-dependent cytotoxicity (ADCC) to chicken RBC (CRBC) were studied. Male BALB/c mice, aged 5-8 wk, were immunized against CRBC by repeated ip injections. The vaccine was prepared from equal wt of BCG cell wall skeletons, trehalose dimycolate (TDM), and mutant Salmonella typhimurium endotoxin (ET) attached to mineral oil microdroplets. The effect of the vaccine or various combinations of its components was tested by injection into immune mice. Spleen cells were then obtained and tested against CRBC. The ADCC of mouse splenocytes increased significantly within 5 days of the vaccine injection and remained elevated as long as 20 days after injection. Splenic leukocyte hypertrophy accompanied the raised ADCC. Injection of 1.5, 15, and 150 ug doses of vaccine produced no enhancement of ADCC at 1.5 ug but an increasing dose-related response at the two higher doses. Most of the ADCC was removed by passing the splenocytes through a Sephadex column. A small amount of the activity remained in the non-adhering fraction. No single component was responsible for the cytotoxic effect of the whole vaccine, but TDM and ET made larger contributions to the overall effect. Absence of mineral oil from the vaccine significantly reduced vaccine activity. (26 Refs)

28. EXPERIMENTAL ANIMAL TUMOR IMMUNOTHERAPY WITH BACTERIAL POLYSACCHARIDE.

Zhao J, Kazuo N
Chemotherapy Div., Natl. Cancer Center Res. Inst., Tokyo, Japan
Chin Med J [Engl]; 94(6):375-378 1981

The carboxymethylated derivative (CM-TAK) of the bacterial polysaccharide (1 leads to 3)-beta-D-glucan was tested as an immunomodulator in 8-wk-old female ICR mice implanted sc with 5 x 10(6) ascitic sarcoma 180 cells on day 0. CM-TAK was injected ip as follows (all groups consisted of 6 mice): 20 mg/kg/day (5x) on days 1, 3, 5, 7, and 9 (Group 1); 100 mg/kg/day on day 1 (Group 2); 100 mg/kg/day on day 7 (Group 3); and 100/mg/kg/day on day 14 (Group 4); Group 5, the controls, received no CM-TAK. Tumors in all test mice grew as in controls until 1 wk after implantation. Then, tumors in Group 1 and 2 showed marked tumor regression, with complete disappearance of the tumors by day 35 in 5/6 Group 1 mice and 4/5 Group 2 mice. Tumors in Group 3 mice continued to grow for 2 wk after implantation (1 wk after CM-TAK treatment) and then regressed. Tumors in Group 4 mice began to regress immediately after treatment, with complete regression in 2/5 mice 21 days after the injection. CM-TAK was most effective when administered in a single large dose 2 wk after tumor implantation. The polysaccharide merits further study as a chemotherapeutic agent. (3 Refs)

29. IN VIVO AUGMENTATION OF NATURAL KILLER (NK) ACTIVITY BY A STREPTOCOCCAL PREPARATION, OK-432: CHARACTERIZATION OF EFFECTOR CELLS AND INDUCTION OF INTERFERON IN SERA.

Wakasugi H, Miyata M, Morioka Y, Oshimi K, Kasahara T, Takahashi K, Saito M, Ebina T
Dept. Surgery, Jichi Medical Sch., Japan
Nippon Gan Chiryo Gakkai Shi; 16(3):433-446 1981

The effects of pre- and/or postoperative treatment with streptococcal preparation OK-432 on natural killer (NK) cell activity and interferon titers were studied in 40 patients with stomach, breast, pancreas, or colon cancer. The patients received a first OK-432 course beginning on postoperative days 7-35 (Group I) or a second course beginning on postoperative days 8-52 (Group II), 6-20 (Group III), or 5-43 (Group IV). Patients in Groups I, II, and III showed significantly augmented killer cell activity within 3 days of initial OK-432 inoculation. Characterization of effector cells from Group IV patients showed that they were NK cells (T and non-T cells and IgG-Fc receptor-positive cells). Induced IF titers studied in Groups I, II, and III did not correlate with levels of augmented NK activity. Four Group III subgroups were distinguished according to degree of NK activity and IF titers: patients with low IF titers that declined with augmented NK activity, patients with low titers that increased with augmented NK activity, patients in whom IF was detected continuously without NK augmentation, and patients with augmented NK activity but no significant IF induction. (40 Refs) (In JPN)

30. STAPHYLOCOCCAL PROTEIN A ENHANCES NATURAL KILLING ACTIVITY AGAINST LYMPHOID TUMOR CELL LINES.

Patel PC, Stefanescu-Soare I, Menezes J
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Int J Cancer; 28(3):277-284 1981

Protein A (pA), was found to augment the natural killing (NK) activity of peripheral blood lymphocytes against Burkitt's lymphoma-derived Raji and Daudi cells. This pA-enhanced NK activity was determined using the 51 Chromium release microcytotoxicity assay. It was found that the increased NK activity was dependent on the concentration of pA used. In addition, the pA-enhanced NK activity was dependent on the time of incubation of pA with the effector and target cell mixture. Pretreatment of effectors for 16 hr or more dramatically increased the NK activity against a wide range of tumor targets of different origin and possessing either B, T or null cell surface characteristics. The presence of the Epstein-Barr virus (EBV)-genome in the target cells did not influence the pA-enhanced NK activity. Nylon-wool column-fractionated, non-adherent lymphocytes (enriched in NK cells) showed an increased NK activity in the presence of pA than unfractionated lymphocytes. Pretreatment of certain targets with pA rendered them more sensitive to NK lysis. Interferon production was readily detected in supernatants from cultures of pA-treated effectors or effector-target mixtures, but not in supernatants from pA-treated target cultures tested. Results of different physicochemical treatments indicate that the pA-induced interferon is of gamma type (Type II). Thus, the data presented suggest that the pA-induced enhancement of NK activity is most likely mediated by the pA-induced interferon. (Author abstract) (26 Refs)

31. CHANGES IN THE PERITONEAL MACROPHAGE CYTOSTATIC ACTIVITY CAUSED BY THE ADMINISTRATION OF IMMUNOPOTENTIATORS AND ANTICANCER AGENTS IN NORMAL AND TUMOR-BEARING RATS.

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Ochanomizu Igaku Zasshi; 29(1):11-22 1981

The peritoneal macrophage cytostatic activity (PMCA) of normal and Sato lung cancer (SLC)-bearing Donryu rats that had been given Nocardia rubra-cell wall skeleton (N-CWS) or BCG as an immunopotentiator and 1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2 chloroethyl)-3-nitrosourea hydrochloride or cyclophosphamide as an anticancer agent was measured and examined for its correlation with antitumor activity. When immunopotentiators were given to normal rats, the effect on the PMCA varied with the type of immunopotentiator and the route, method and period of administration. The increase in in vitro cytostatic activity correlated well with the results obtained by in vivo Winn-type neutralizing tests. The PMCA of the tumor-bearing rats was lower than that of the control rats, but was restored or even improved by the administration of immunopotentiators. When anticancer drugs were given to normal rats, the decrease in macrophage function was prevented by the simultaneous administration of immunopotentiators. The tumor growth-inhibiting effect of immunochemotherapy in tumor-bearing rats was stronger than that of immunotherapy or chemotherapy given alone. On the other hand, PMCA was also markedly increased in the rats given immunochemotherapy, which suggests that potentiated macrophages play a role in the antitumor effect of immunochemotherapy. (42 Refs) (In JPN)

CYTOKINE THERAPY

32. THE ROLE OF INTERLEUKIN-2 (IL-2) IN THE DIFFERENTIATION OF CYTOTOXIC T CELLS: THE EFFECT OF MONOCLONAL ANTI-IL-2 ANTIBODY AND ABSORPTION WITH IL-2 DEPENDENT T CELL LINES.

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J Immunol; 127(4):1323-1328 1981

A variety of approaches, including the use of a monoclonal antibody, have indicated that the lymphokine interleukin 2 is a necessary and sufficient mediator for initiating cytotoxic T cell differentiation in vitro. Mitogen (Con A, PHA) stimulation of spleen cells and K/D or I region stimulation in primary MLC all led to IL-2 production, as measured by the growth of an IL-2 dependent T cell clone, and to the production of a 'helper' factor necessary for cytotoxic T lymphocyte (CTL) differentiation against metabolically inactivated stimulator spleen cells. Several lines of evidence suggested that the IL-2 activity and CTL 'helper' activity were due to a single molecular entity. These included the observations that: (i) there was a linear relationship (R = 0.99) between IL-2 activity and relative CTL 'helper' activity regardless of the preparation used (purified IL-2; MLC, or mitogen-induced supernatants). (ii) Absorption of MLC supernatants with T cell 'blasts' or with IL-2 dependent T cell lines concomitantly removed both IL-2 and CTL 'helper' activities, (iii) IL-2 activity purified by isoelectric focusing, or by polyacrylamide gel electrophoresis, displayed CTL 'helper' activity. (iv) Both CTL 'helper' and IL-2 activities were neutralized by a monoclonal antibody directed against IL-2. (Author abstract) (21 Refs)

ACTIVE SPECIFIC IMMUNIZATION

33. MORPHOLOGICAL AND FUNCTIONAL ASPECTS OF ACTIVE SPECIFIC IMMUNOTHERAPY OF ESTABLISHED PULMONARY METASTASES IN GUINEA PIGS.

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Cancer Res; 41(10):4001-4009 1981

Using active specific immunotherapy, we evaluated the efficacy of syngeneic tumor cell vaccines supplemented with the adjuvant Mycobacterium bovis strain BCG against established pulmonary metastases. In a series of experiments, inbred strain 2 guinea pigs were given iv injections of 10(6) syngeneic hepatocarcinoma cells (100x the minimum lethal dose). Animals were not treated or were treated once a wk for 2 wk with vaccines consisting of 10(7) cryopreserved, x-irradiated viable tumor cells admixed with 10(7) live BCG and on the 3rd wk with a vaccine consisting of 10(7) tumor cells alone. To assess the limits of tumor burden in this model, we immunized groups of animals on days 1, 4, 7, or 10 after iv tumor challenge. The pulmonary tumor foci ranged from clumps of several cell at day 1 to nodules between 0.1 and 0.2 mm in diameter at day 10. By days 21 to 24 after iv tumor challenge, the pulmonary nodules were macroscopic in size, equal to or greater than 0.5 mm in diameter. While significant protection was measured by survival, the effectiveness of this combination of tumor cells plus BCG was limited by tumor burden. Morphological evaluation of pulmonary tumor foci in treated animals revealed mononuclear cell infiltration characteristic of a cell-mediated hypersensitivity reaction in the time interval between the first and second immunization. By the time of the third immunization, the nodules had progressed to a marked histiocytosis with fibrosis and central necrosis. It is possible not only that these specific immunological reactions accomplish a significant reduction of the tumor mass but that the host-mononuclear cell infiltrate disrupts the organized histological architecture of metastatic clones, perhaps by the release of soluble factors such as lymphokines. This disruption of the organized histological architecture of the metastatic clones creates a state in which the tumor cells may be more vulnerable or exposed, by destroying the anatomic barriers that allow the tumor to escape disruption by a variety of antitumor agents. This report suggests that multimodality therapy such as postsurgical active specific immunotherapy would be enhanced in combination with other antitumor agents, which on their own would be limited by the anatomical organization of micrometastatic nodules. (Author abstract) (48 Refs)

ADOPTIVE IMMUNIZATION AND RELATED APPROACHES

34. TRANSFER FACTOR IN THE TREATMENT OF HERPES SIMPLEX TYPES 1 AND 2.

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Dermatologica; 163(2):177-185 1981

Transfer factor potentiates cellular immunity and induces interferon. It was because of these properties that transfer factor was tried in 17 patients with recurrent herpes simplex types 1 and 2. Transfer factor was administered in doses ranging from 5 to 10 U/m2 im. The interval between injections varied from 1 wk to 3 mo. Sixteen patients could be evaluated clinically in whom the recurrence rate decreased from 10.7 +-6.1 to 2.1 +-2.5 (mean SD). The reduction was statistically significant. Eight patients were completely free of disease while the other eight had a reduced number of episodes during the period of observation. Seven patients had abnormal T cell function as reflected by the low number of T cells or low lymphocyte transformation. Statistically significant improvement in the T cell function was observed. Delay ed hypersensitivity skin test reactions also improved significantly. (Author abstract) (17 Refs)

35. TRANSFER OF ANTITUMOR IMMUNITY WITH RIBONUCLEIC ACID-CONTAINING SPLEEN EXTRACT OF IMMUNIZED ANIMALS. IN VIVO TRANSFER OF TUMOR IMMUNITY AGAINST MOUSE MAMMARY CARCINOMA.

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Cancer Immunol Immunother; 11(3):189-193 1981

The combined effect of ribonucleic acid-containing spleen extract and live bacterial cells of an attenuated strain of Salmonella on tumor growth in recipient mice was studied. Mammary carcinoma Ca755 tumors were implanted in C57BL/6 mice, removed after 10 days, and retransplanted at appropriate times later. RNA was extracted from the spleens of mice that demonstrated resistance to the retransplantation (i-extract), and from spleens of untreated mice (n-extract). Additional mice were injected sc with 1 x 10(6) tumor cells/mouse, attenuated Salmonella enteritidis (SER: 1 x 10(5) cells/mouse), i-extract, and/or n-extract. Tumor growth was inhibited in mice receiving SER 6 days prior to tumor cell injection or i-extract 6 days after tumor cell injection. Inhibition of tumor growth was synergistically increased by SER given 6 days prior to, and i-extract given 6 days after, tumor cell injection. SER injected at or after the time of tumor cell injection had no effect. N-extract also had no effect. I-extract had no effect when injected prior to or at the same time as tumor cell injection. The results demonstrated presence of some factor which transfers immunity from donor to recipient mice. Injection of live attenuated SER stimulates a non-specific immune response which can act synergistically with the transferable factor. (13 Refs)

36. ADOPTIVE IMMUNOTHERAPY AND COMBINED CHEMO-IMMUNOTHERAPY IN TRANSPLANTABLE LEUKAEMIA OF AKR MICE (TAL); OCCURRENCE OF NATURAL KILLERS.

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Haematologia (Budap); 14(2):137-146 1981

Inbred AKR mice received transplantable AKR leukemia (TAL: 10(4)-10(5) viable lymph node cells from ill syngeneic donors) by ip injection. Effector cells were obtained from C57BL/6, DBA/2J, BALB/c, or syngeneic AKR donors. Some allogeneic donors had been preimmunized with AKR cells. Some recipients received donor cells irradiated before injection. Some received whole-body x-ray irradiation (300 rad) before injection of tumor cells. Intact mice injected with TAL, but not otherwise treated, survived longer than irradiated mice. Injection of allogeneic effector cells from non-immunized mice increased the survival time of intact TAL-bearing mice. Syngeneic effector cells had no effect. Thymocytes from non-immunized donors or lymph node cells from immunized donors increased survival time in irradiated mice. Injection of 50 mg/kg cyclophosphamide (CY) produced a 70% permanent survival rate. Injection of effector cells did not increase the effect of CY. Thymocytes from immunized or non-immunized donors increased survival time of mice not given CY. Mean survival increased as effector cell:target cell ratio increased from 10:1 to 1,000:1. Above 1,000:1 no increase was noted. Results indicate the existence of natural non-immune cytotoxic cells, directed against Gross virus-infected cells, in C57BL/6, DBA/2J, and BALB/c mice, but not in AKR mice. These effector cells were present in many lymphoid organs. (31 Refs)

37. ERADICATION OF DISSEMINATED MURINE LEUKEMIA BY CHEMOIMMUNOTHERAPY WITH CYCLOPHOSPHAMIDE AND ADOPTIVELY TRANSFERRED IMMUNE SYNGENEIC LYT-1 + 2- LYMPHOCYTES.

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J Exp Med; 154(3):952-963 1981

The efficacy of T cell subpopulations, as distinguished by expression of Lyt antigens, was analyzed in adoptive chemoimmunotherapy (ACIT) of established murine leukemia and in in vitro assays for the generation and expression of cytotoxicity. The results demonstrated that the predominant donor effector cell required for eradication of advanced disseminated leukemia by ACIT is an immune Lyt-1 + 2-T cell that is not cytolytic in vitro. Immune cells depleted of Lyt-2+ cells, such that the only donor T cells remaining were of the Lyt-1 + 2-phenotype, were nearly as effective in ACIT as unselected cells suggesting that other donor T cell subsets do not provide an essential contribution. The potential therapeutic efficacy of immune cells was ablated nearly as completely by depletion of Lyt-1+ cells as by depletion of all T cells. The small residual anti-tumor effect still evident after treatment of immune cells with alpha-Thy-1.2 and complement probably reflected incomplete T cell removal. The T cell subset analyzed in ACIT were defined operationally by susceptibility to lysis by monoclonal antibody to Lyt antigens and complement. The results demonstrated that the phenotype of the predominant T cell subset required for efficacy in ACIT is Lyt-1+2-, which is distinct from the T cell phenotypes mediating in vitro tumor lysis. The mechanisms by which Lyt-1 + 2-cells can promote tumor rejection are discussed. (31 Refs)

38. AN EXPERIMENTAL STUDY OF PASSIVE CANCER IMMUNOTHERAPY BY INFUSION OF IMMUNE LYMPHOCYTES.

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Nippon Geka Gakkai Zasshi; 82(3):193-202 1981

Experiments were first carried out to see whether cryoimmunity for cancer is induced. The tumors of rats were treated by freezing, and their peripheral lymphocytes were collected and infused into other rats. We observed by the challenge of the same tumor cells and macrophage migration inhibition test whether antitumor activity was transferred to these rats. The rats receiving the infusion rejected the tumor challenge at a high frequency. The lymphocytes collected from these rats specifically inhibited the migration of macrophages. From these results, the establishment of cryoimmunity in the primary rats was proved. Further experiments were carried out to evaluate the effects of the same lymphocytes infused into the tumor-bearing rats. Remarkable inhibition of tumor growth and elongation of mean survival days were observed. These effects depend on the dose of infused lymphocytes. Remarkable infiltration of lymphocytes in the tumor tissue after infusion was seen by means of histological study. (28 Refs) (In JPN)

OTHER BIOLOGICAL RESPONSE MODIFIERS

39. THE EFFECT OF NUTRITIONAL SUPPORT ON IMMUNE COMPETENCY IN PATIENTS SUFFERING FROM TRAUMA, SEPSIS, OR MALIGNANT DISEASE.

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Surgery; 90(4):610-615 1981

Thirty-nine patients, 25 of whom were suffering from trauma, sepsis, or malignant disease, were studied prospectively to determine the immunologic value of improved protein-cal balance in this setting. All were suffering from varying degrees of malnutrition, and 72% (p less than 0.05) of the patients with anergy-inducing disease processes were anergic at the time of evaluation. In the presence of disease-induced anergy, skin test reactivity was not helpful in measuring the therapeutic response to nutritional support; however, among severely wasted patients, significant elevations in absolute lymphocyte count and serum albumin suggest that these are useful parameters when following the severely wasted patient who has concomitant trauma, sepsis, or malignant disease. (Author abstract) (13 Refs)

40. INFLUENCE OF TOTAL PARENTERAL NUTRITION (TPN) ON SOME IMMUNE PARAMETERS IN MALNOURISHED SURGICAL PATIENTS.

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Acta Chir Belg; 80(2/3):149-155 1981

The effect of total parenteral nutrition (TPN) containing Intralipid on some immune parameters of 21 protein-depleted surgical patients (9 men, 12 women) was evaluated. The disorder treated included neck and digestive tract neoplasms, digestive fistula, inflammatory bowel disease, gastric ulcer, burns over 40% of body area, and massive intestinal resection. The evolution of these immune parameters were studied in relation to nitrogen balance. An attempt was made to determine an eventual specific immune response towards fat emulsion or a direct immunostimulatory or inhibitory property exhibited by exogenous lipids. No adverse reaction was observed in any of these 49 patients during TPN. On wk of TPN resulted in a positive cumulative nitrogen balance in 7/21 patients, a negative balance in 9/21, and no change in 5/21. Before TPN, lymphocyte response to phytohemagglutinin (PHA) was abnormally low in 18/21 patients, while levels of immunoglobulins and isohemagglutinins were normal in all 21. In the seven patients with a positive nitrogen balance following TPN the mean lymphocyte response to PHA increased and became normal in 2/7. Of the five patients with unchanged nitrogen balance, lymphocyte performance was improved in 3/5, decreased in 1/5, and unchanged in 1/5. In the nine patients with a negative nitrogen balance after TPN treatment, the mean lymphocyte response to PHA was not significantly modified. The in vitro or in vivo addition of Intralipid had no effect on lymphocyte response. The results indicated that TPN may improve the prognosis of surgical depleted patient by correcting some previously altered immune parameters as well as nitrogen balance. (30 Refs)

41. ANTITUMOR ACTIVITY OF HOT WATER EXTRACT OF DANDELION, TARAXACUM OFFICINALE - CORRELATION BETWEEN ANTITUMOR ACTIVITY AND TIMING OF ADMINISTRATION.

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Yakugaku Zasshi; 101(6):538-543 1981

Antitumor effects of a non-dialyzable hot water extract, Tof-CFr, that was isolated from dandelions (Taraxacum officinale), were investigated with ICR, ddY, and C3H/Hef mice bearing Ehrlich and MM46 ascites tumors or sarcoma 180 tumors. The antitumor effects of the Tof-CFr were compared with those produced by administration of lentinan and yeast mannan. Following sc transplantation of tumor cells in the mice, the Tof-CFr, lentinan, and yeast mannan were administered daily on days 1-10, or on days 11-20, or every other day on days 2-20 in doses of 20-60 mg/kg, 1.7 mg/kg, and 60 mg/kg, respectively. Day 35 after transplantation, the tumors were resected and the tumor wt was determined. The Tof-CFr had antitumor effects on the allogeneic ddY-Ehrlich tumor system and on the syngeneic C3H/Hef-MM46 tumor system when administered days 11-20 or 2-20 but not if administered days 1-10. For the lentinan and the yeast mannan, timing of administration was important only for the ddY-Ehrlich system. The Tof-CFr showed cytolytic activation of macrophages in antibody-dependent macrophage mediated cytolysis and enhanced antitumor delayed hypersensitivity reactions in the ddY-Ehrlich and C3H/Hef-MM46 systems, suggesting a tumor growth-inhibiting action similar to that of lentinan. (10 Refs) (In JPN)

ANIMAL MODELS OF BIOLOGICAL THERAPY

42. A DISTRIBUTION-FREE TEST FOR TUMOR-GROWTH CURVE ANALYSES WITH APPLICATION TO AN ANIMAL TUMOR IMMUNOTHERAPY EXPERIMENT.

Koziol JA, Maxwell DA, Fukushima M, Colmerauer ME, Pilch YH
Dept. Mathematics and Medicine, Univ. California, San Diego, La Jolla, CA, 92093
Biometrics; 37(2):383-390 1981

A distribution-free statistical methodology for the comparison of growth curves is described. This procedure may be used with incomplete observations, and in situations where parametric models for growth may not be appropriate. Data from an experiment to investigate various immunotherapy regimens for solid tumors are presented, and then analyzed by this technique. (Author abstract) (21 Refs)

CLINICAL IMMUNOLOGY

43. CIRCULATING IMMUNOCOMPLEXES IN LEUKEMIA.

Mod A, Carpentier N, Fust Gy, Lambert PH, Miescher P, Hollan Zs
Orszagos Haematologial es Vertranszfuzios Intezet, Budapest, Hungary
Orv Hetil; 122(29):1757-1762 1981

The circulating immunocomplex (CIC) levels were determined in the blood serum of 113 patients with leukemia by three different methods (125 I-C1q-binding test, complement consumption test, and C1q solubility test). Acute myeloid leukemia was diagnosed in 54 cases, acute lymphocytic leukemia in 11, chronic myelocytic leukemia in 22, and acute lymphocytic leukemia in 26. Increased CIC level was demonstrated by at least two of the three tests in 64% of the patients. The repeated determinations revealed a relationship between the immunocomplex level and the stage of the disease: the CIC level was higher during blast crisis than during remission. The CIC levels were often increased during infections as well. The CIC level also showed fluctuations regardless of the clinical picture, and the fluctuations demonstrated by the different test methods often failed to parallel with one another. The findings suggest that the circularing immunocomplexes occurring in leukemias are heterogeneous and their composition is subject to variations in the course of the disease. (25 Refs) (In HUN)

44. INVERSE CORRELATION OF ANTIVIRAL ANTIBODY TITERS AND THE REMISSION LENGTH IN PATIENTS TREATED WITH VIRAL ONCOLYSATE: A POSSIBLE NEW PROGNOSTIC SIGN IN ACUTE MYELOGENOUS LEUKEMIA.

Schuepbach J, Sauter C
(c/o Sauter) Div. Oncology, Dept. Medicine, Univ. Hosp., Ramistrasse 100, 8091 Zurich, Switzerland
Cancer; 48(6):1363-1367 1981

In a study conducted since August 1974 by the Swiss Group for Clinical Cancer Research, 57 of 107 patients suffering from acute myelogenous leukemia achieved a complete remission. Thirty of these 57 patients were randomly selected to receive maintenance chemotherapy alone; the other 27 patients received, in addition to the same chemotherapy, monthly injections of viral oncolysate (ie, formalin-treated fowl plague virus-infected allogenous leukemia cells). The levels of antifowl plague virus antibody titers in the sera were determined at regular intervals. All patients with an initial antibody tite r of zero and a titer increase after the very first injection of oncolysate had remission times of less than 6 mo (p less than or equal to 0.02). After the fifth injection there was a clear reverse correlation of titer values and remission lengths (p less than or equal to 0.01). Several patients showed an association of changes of antiviral antibodies in the serum and the percentage of myeloblasts in the bone marrow. Immunization by viral oncolysate can therefore be used to predict the course of patients who are in remission from acute myelogenous leukemia; it may furthermore be helpful in detecting patients whose treatment has been insufficient. (Author abstract) (16 Refs)

45. DETECTION OF ANTIBODIES AND ANTIGENEMIA IN LEUKEMIC PATIENTS WITH CANDIDIASIS BY ENZYME-LINKED IMMUNOSORBENT ASSAY.

Meckstroth KL, Reiss E, Keller JW, Kaufman L
(c/o Reiss) Mycology Div., Centers for Disease Control, Atlanta, GA, 30333
J Infect Dis; 144(1):24-32 1981

Standard tests and two enzyme-linked immunosorbent assays (ELISAs) were compared for detecting systemic candidiasis in 92 leukemic patients. Antibodies to Candida were detected by immunodiffusion (ID), latex agglutination (LA), and indirect ELISA; antigenemia was evaluated by indirect ELISA inhibition. In 48 patients without candidiasis (Group 1), sera from 27% reacted in ID and 13% in LA tests; titers of antibody by ELISA occurred in all patients. In 34 patients without disseminated candidiasis (Groups 2 and 3), Candida species were isolated; sera from 35% and 32% were positive in the ID and the LA test, respectively. In 9 of 10 patients with disseminated candidiasis (Group 4), LA and ID tests were negative. Seven patients in Groups 1-3 without disseminated candidiasis were antigenemic (false-positive rate, 9%). Antigenemia was detected in 7 of 10 patients with disseminated candidiasis; in the remaining three patients sera were drawn too early to be of diagnostic value. Thus, monitoring of immunosuppressed patients for mannan antigenemia is useful for the detection of disseminated candidiasis. (Author abstract) (12 Refs)

46. IN VITRO PRODUCTION OF HUMAN ANTIBODY TO A TUMOUR-ASSOCIATED FOETAL ANTIGEN.

Irie RF, Jones PC, Morton DL, Sidell N
Div. Oncology, Univ. California Sch. Medicine, 54-140 CHS, Los Angeles, CA, 90024
Br J Cancer; 44(2):262-266 1981

After the establishment of lymphoblastoid cell lines that synthesize antibody directed against a human tumor-associated fetal antigen designated as oncofetal antigen-I (OFA-I), a method is described for the production of IgM anti-OFA-I in vitro. Ten serum samples containing high levels of anti-OFA-I were identified and viably frozen peripheral-blood lymphocytes (PBL) from the same patients were transformed by Epstein-Barr virus (EBV). Patients included five given adjuvant immunotherapy with an OFA-I+ tumor-cell vaccine (TCV), three treated with BCG, and two treated only by surgical excision. Anti-OFA-I levels in the spent medium were monitored by immune-adherence using the OFA-I+ melanoma cell line UCLA-SO-M14 (M14), as the target cell. Two of the EBV-infected cultures (ES from the TCV group and CD from the surgery only group) produced detectable antibody to M14 cells by day 6. By day 9, culture DV (BCG group) became positive. The CD culture was positive only for 9 days, while ES (obtained from the patient with the highest anti-OFA-I titer) ceased growth after 3 wk. The supernatants displayed no reactivity against a control lymphoblastoid cell line autologous to the M14 donor. The DV lymphoblasts continued to produce increasing titers of anti-M-14 antibody until day 42, with gradual decrease by day 60 and became negative on day 66. None of the other 7 PBL cultures became positive to M14. Further studies determined that the antibody exhibited specific reactivity to an antigen associated with human cancer. No antibody reactivity in the DV culture medium was detected to a number of target cells tested. Assessment of the immunoglobulin class indicated the anti-OFA-I was limited to the IgM class. The DV spent medium was cytotoxic in the presence of either rabbit or human complement. (21 Refs)

REVIEWS

47. PHARMACOKINETIC STUDIES OF INTERFERONS.

Bocci V
Inst. General Physiology, Univ. Siena, 53100 Siena, Italy
Pharmacol Ther; 13(3):421-440 1981

The behavior of the various types of interferon (IF) from human sources in the human body in consequence of dilution, cell binding, and catabolism is reviewed. General considerations of the metabolism of IFs are discussed, including the need for homogeneous IF and a radioimmunoassay for IF, and problems with the rapid metabolism of IF. The question of whether IF binding to the cell receptor represents a first catabolic step is addressed, as are the catabolic roles of the liver, kidney and muscle; the metabolic role of the endothelial cells; whether any IF leaks into the gastrointestinal lumen, whether the lung has any catabolic role; and the role of neutrophils and mononuclear phagocytes. An attempt was made to present a conceptual framework to be used for future pharmacokinetic studies. It appears that the most sialylated IF, particularly without any exposed galactose, should be the least susceptible to hepatic uptake and renal filtration. Further studies should be directed at defining the factors controlling distribution, uptake or metabolism of IF so that it can be applied more readily and successfully in human and veterinary medicine. (200 Refs)

48. USAGES OF INTERFERON AND INTERFERON INDUCERS IN MAN: THE SECOND HALF OF 1980.

Pollard RB
Dept. Medicine, Univ. Texas Medical Branch, Div. Infectious Diseases, Galveston, TX
Med Biol; 59(2):69-76 1981

Utilizing the systematic nomenclature for interferons used in research and clinical trials, some aspects of human leukocyte interferon (HuIFN-alpha) and human fibroblast interferon (HuIFN-beta) are reviewed. HuIFN-alpha is discussed with respect to its effects on herpes simplex virus and Epstein-Barr virus infections, its effects on hepatitis B virus and other virus infections in patients treated for other disorders, its effects in malignancy, its cellular effects, and its effects in miscellaneous disorders (Creutzfeldt-Jacob disease, schizophrenia, and psychotic depression). HuIFN-beta is reviewed with respect to its effects on various virus infections (such as rhinovirus and adenovirus infections) and the cutaneous reactions and side effects that are observed in its use. The association of keratopathy, significant retinal mottling, and arteriolar narrowing (related to decrease in visual field size) with the administration of the interferon inducer tilorone is documented. Implications of some of the reported findings are discussed. (22 Refs)

49. AN OVERVIEW OF IMMUNOTHERAPY, ESPECIALLY OF BREAST CANCER.

Gottlieb AA
Dept. Microbiology and Immunology, Sch. Medicine, Tulane Univ., New Orleans, LA, 70112
Comment Res Breast Dis; 2:103-132 1981

Immunotherapy, particularly as applied to treatment of breast cancer, is reviewed. Parameters of immune responsiveness to breast cancer, such as lymphocyte transformation and infiltration, response to skin test antigens, and peripheral lymphocyte counts, are described. The nature of viral antigens in breast cancer is discussed. Suppressors and suppressor cells, including non-T cell suppressor cells, are discussed. Active, adoptive, and passive immunotherapies are detailed, including use of Corynebacterium parvum, BCG, levamisole, immune RNA, interferon, glucan, and transfer factor. Future research into the isolation of those components of biological agents, such as BCG and C parvum, which produce particular effects on immune response, is urged. (127 Refs)

50. NATURAL KILLER CELLS: THEIR ROLE IN DEFENSES AGAINST DISEASE.

Herberman RB, Ortaldo JR
Lab. Immunodiagnosis, NCI, Bethesda, MD, 20205
Science; 214(4516):24-30 1981

Natural killer cells are a recently discovered subpopulation of lymphoid cells that are present in most normal individuals of a range of mammalian and avian species. Natural killer cells have spontaneous cytolytic activity against a variety of tumor cells and some normal cells, and their reactivity can be rapidly augmented by interferon. They have characteristics distinct from other types of lymphoid cells and are closely associated with large granular lymphocytes, which comprise about 5% of blood or splenic WBC. There is increasing evidence that natural killer cells, with the ability to mediate natur al resistance against tumors in vivo, certain virus and other microbial diseases, and bone marrow transplants, may play an important role in immune surveillance. (Author abstract) (105 Refs)

51. CANCER AND SUBVERSION OF HOST DEFENCES.

Nelson DS, Nelson M, Farram E, Inoue Y
Kolling Inst. Medical Res., Royal North Shore Hosp., St. Leonards, N.S.W. 2065, Australia
Aust J Exp Biol Med Sci; 59(part3):229-262 1981

The relationship between cancer and the immune system is reviewed. Effector cells, defects in cell-mediated and humoral immunity in cancer patients, immune defects in experimental animals, stimulation of macrophages and other cells, and the subversion of host defenses by viruses are discussed. Soluble products of tumor cells, which may act directly on the cell or mediators involved in inflammation or indirectly by way of the immune system, seem to be key factors in the subversion of host defenses. Tumors may also subvert host defenses by inducing suppressor cell production. The ability of a host to promote tumor growth, interactions between the clotting systems and cell-mediated immunity, and activated macrophages serving as antitumor effector cells are described. It was suggested that there is a great deal of evidence that tumors can depress or subvert various components of the host's immune system. (268 Refs)

52. CANCER IMMUNOPROPHYLAXIS: A CAREFUL DIALOGUE.

Hollinshead AC
Div. Oncology, Dept. Medicine, George Washington Univ. Medical Center, Lab. for Virus and Cancer Res., Washington, DC, 20037

Cancer Detect Prev; 3(2):419-448 1981

The role of immunology in prevention, screening, and early detection of cancer is reviewed. Lung cancer immunotherapy trials with purified tumor-associated antigens (TAA) are described. In the first trial, patients with Stage I lung cancer received methotrexate (MTX: 300 mg rapid iv and 700 mg infused over 6 hr), TAA (500 ug) emulsified with Freund's complete adjuvant (FcA), or MTX + TAA with FcA. Of 24 nonimmunized patients, 4/8 on chemotherapy and 8/16 with no therapy died; of 28 immunized patients, 4/15 on immunotherapy and 4/13 on immunochemotherapy died. At 4 yr, 80% of the immunized group is alive compared with 50% of the control group. In a second trial, patients with Stages I and II squamous cell lung cancer were treated by curative resection alone (27 patients), resection followed by TAA with FcA (24), or resection followed by adjuvant and antigen injected in separate sites (29). The 3-yr survival of these groups is 35%, 85%, and 90%, respectively. Patients reacted to allogeneic and autologous TAA, and TAA vaccination induced strong delayed hypersensitivity reactions that lasted as long as 5 yr. Characteristics of TAA which induce cell-mediated immunoresponses are discussed. TAA immunoprophylaxis is recommended for groups at high risk for lung cancer. (54 Refs)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HE 20. 3173/2:

CLINICAL TRIALS

1. A PHASE I STUDY OF HUMAN LYMPHOBLASTOID INTERFERON IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES.

Rohatiner A, Balkwill F, Malpas JS, Lister TA
Dept. Medical Oncology, St. Bartholomew's Hosp., West Smithfield, London EC1A 7BE, England
Haematol Blood Transfus; 26:63-67 1981

Preliminary results of a Phase I study of human lymphoblastoid interferon (HLBI) in patients with acute myeloblastic leukemia (AML: 10), follicular non-Hodgkin's lymphoma (1), myeloma (1), and chronic lymphocytic leukemia (1) are described. All patients complained of general malaise and anorexia, and became pyrexial between 2 and 24 hr after administration of HLBI. Of the 13 patients, 4 complained of rigors, 3 of headaches, and 1 of joint pains. One patient experienced a hypotensive episode after the second injection of HLBI. All patients had bone marrow infiltration rendering interpretation of the blood count extremely difficult. In patients with AML, a fall in Hb and platelet counts was compatible with advancing disease. No evidence of renal impairment was found; liver function tests remained normal. Serum interferon activity was measured. The results indicated that up to 10 x 10(6) unit/square meter iv can be given daily; to avoid toxicity and achieve consistent levels, iv HLBI should be given by continuous infusion. After iv injection of HLBI, high peak levels were achieved at 30 min, but interferon was rapidly cleared in the first hr after injection. When given by continuous iv infusion, interferon levels increased over 72 hr and then remained elevated. Results of the in vitro study confirmed the cell growth inhibitory effects of HLBI on human myeloblasts. The degree of growth inhibition was dose dependent. However, the concentration of interferon that resulted in 50% inhibition of growth in vitro was 3-10x higher than the serum levels attained. (7 Refs)

2. TREATMENT OF RECURRENT LARYNGEAL PAPILLOMATOSIS WITH AN ARTIFICIAL INTERFERON INDUCER (POLY ICLC).

Leventhal BG, Kashima H, Levine AS, Levy HB
Johns Hopkins Oncology Center, 3-121, 600 N. Wolfe St., Baltimore, MD, 21205
J Pediatr; 99(4):614-616 1981

The synthetic interferon inducer poly ICLC, a complex of high-mol wt poly inosinic-poly cytidylic acid with low-mol wt poly-L-lysine and carboxymethyl cellulose, was used to treat two patients (5-yr-old boy and 4-yr-old girl) with highly aggressive forms of recurrent laryngeal papillomatosis. The boy presented with extensive papillomatosis of the larynx and trachea, and bilateral nodular and cavitating lesions in the lung. Throughout a 12-wk course of poly ICLC (12 mg/square m (m2), 3x/wk) no surgery was required. On maintenance poly ICLC therapy, he required operations approx 1x/3 mo. His pulmonary lesions did not regress. Symptoms of toxicity consisted of fever, nausea, and vomiting, with occasional headache for 24 hr after each dose. The other patient had 3 mo of poly ICLC (12 mg/m2) therapy 3x/wk, followed by a 3-mo course at 12 mg/m2 weekly. During this 6-mo period, she required surgery 7x; no change occurred in her chest radiography. Poly ICLC therapy was discontinued and in the next 2 mo she required surgery 5x. Poly ICLC (12 mg/m2/wk) was restarted, and the frequency of operative interventions again fell to 1x/4-5 wk. The patient exhibited nausea with fever during each course of therapy. The interferon levels of both patients reached as high as 3,000 units. (10 Refs)

3. FOLLOW-UP OBSERVATIONS ON THE EFFECT OF HUMAN LEUKOCYTE INTERFERON IN NON-HODGKIN'S LYMPHOMA.

Louie AC, Gallagher JG, Sikora K, Levy R, Rosenberg SA, Merigan TC
Div. Oncology, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Blood; 58(4):712-718 1981

Follow-up data for 11 patients with non-Hodgkin's lymphoma treated with partially purified human leukocyte interferon is presented. The interferon preparation used was 0.1% pure and treatment consisted of 5 x 10(6) U given im twice daily for 60 injections. One complete, three partial, and three minimal responses were observed in five of seven evaluable patients with nodular non-Hodgkin's lymphoma. Duration of response appears to be from 6 to 12 mo. One patient achieved a second partial response on retreatment with interferon in spite of having received chemotherapy in the interval between interferon treatments. No responses were seen in three patients with rapidly progressive diffuse histiocytic lymphoma. Dose-limiting toxicity is leukopenia, which necessitated modification or cessation of treatment in three patients. Nonhematologic toxicities consisted of fever, malaise, arthralgia, and loss of appetite. In conclusion, interferon has activity against non-Hodgkin's lymphoma, and prior treatment with chemotherapy does not preclude a response to interferon. (Author abstract) (13 Refs)

4. EFFECTS OF INTRALESIONAL INTERFERON ON NEUROBLASTOMA: CHANGES IN HISTOLOGY AND DNA CONTENT DISTRIBUTION OF TUMOR MASSES.

Sawada T, Takamatsu T, Tanaka T, Mino M, Fujita K, Kusunoki T, Arizono N, Fukuda M, Kishida T
Dept. Pediatrics, Kyoto Prefectural Univ. Medicine, Kamikyoku, Kyoto 602, Japan
Cancer; 48(10):2143-2146 1981

Local injections of interferon, 30 x 10(4) IU, 10x, were found to reduce masses of neuroblastoma. Histologic findings and nuclear DNA measurements of cells from tumors in which interferon has been injected compared with cells from tumors that did not receive injections demonstrated that the reduction of neuroblastoma masses by interferon did not depend on increased cell differentiation or on interruption of tumor cell production. Although the mechanism of interferon's action on reducing neuroblastoma is unknown, the disappearance of tumor cells may be caused by high levels of interferon in tumor tissues. (Author abstract) (8 Refs)

5. INTRATUMOURAL ADMINISTRATION OF INTERFERON IN MALIGNANT GLIOMAS (MEETING ABSTRACT).

Salford LG, Stromblad LG, Nordstrom CH, Hornmark-Stenstam B, Brandt L, Brismar J, Brun A, Sjogren HO, Flodgran P
Department of Neurosurgery, University Hospital, Lund, Sweden
Acta Neurochir; 56(1/2):130 1981

We have hitherto given interferon intratumorally to 2 patients with advanced malignant gliomas-one 45-yr-old man with an astrocytoma grade III in the left parietal lobe, and one 53-yr-old woman with an astrocytoma grade III-IV in the right temporal lobe. Both had earlier been subjected to extensive resection of the tumor, followed by chemotherapy (lomustine, procarbazine and vincristine). Both had later developed clinical signs of recurrence, and computed tomographic examinations revealed large tumors. In both patients a Rickham reservoir was placed with its catheter tip in the center of the tumor.

Four x 10(6) units of human WBC interferon, was given daily in the reservoir and 4 x 10(6) units simultaneously im. During therapy both tumos grew, and because of raised intracranial pressure both patients had to be operated upon after about two wk. The parietal tumor of the man could be only partly resected, and his preoperative symptoms, hemiplegia, and dysphasia, were aggravated. The interferon therapy was continued for two mo intratumorally and im. One mo later the patient died because of edema surrounding the tumor. Postmortem examination revealed remarkably large central necrosis in the tumor, surrounded by granulation tissue. The temporal tumor of the woman was extensively resected. Both intratumoral and im interferon injections were given daily for two mo postoperatively. She was in very good shape and during the following three mo she had only im injections. At the end of this period she developed a second recurrence and was reoperated on. The tumor was now on all sides separated from the surrounding brain by a capsule. After the last resection of the large tumor, the patient is in good condition and without signs of metastases. Serial determinations of natural killer (NK) activity were performed in both patients, and revealed a 30-40 per cent increase compared to pretherapeutic levels throughout the courses of interferon treatment. In the woman specific autologous cell-mediated cytotoxicity is presently being studied. (no Refs)

6. BCG-VACCINATION, ITS INFLUENCE ON COURSE AND LETHALITY OF LEUKEMIA.

Ambrosch F, Wiedermann G, Krepler P, Kundi M, Ambrosch P
Institut fur Spezifische Prophylaxe und Tropenmedizin der Univ., Kinderspitalgasse 15, A-1095 Wien, Austria
Fortschr Med; 99(35):1389-1393 1981

As a retrospective study the clinical data of 613 leukemic children were collected. 269 of them were born in Austria, fell sick between 1967 and 1976 and were not older than 5 yr at the onset of disease. BCG-vaccination, which is performed in Austria within the first 3 days after birth, was checked by means of hospital reports, birth protocols and central BCG record. All data were stored and evaluated by electronic data processing. Besides a significant decrease of mortality, which we could dem onstrate in earlier studies, the following correlations between BCG-vaccination of newborn and leukemia were found: Reduction of morbidity, decrease of case fatality, increase of 5 yr survival rate, increase of mean survival time, delayed onset of disease, decrease of frequency of myeloid and chronic leukemia. With the exception of the slight reduction of morbidity all correlations are significant. (Author abstract) (no Refs) (In GER)

7. RESULTS OF ADJUVANT BCG IMMUNOTHERAPY IN MALIGNANT MELANOMA.

Watzig V, Knopf B
Universitats-Hautklinik, Erfurterstrasse 35, DDR-6900 Jena, E. Germany
Arch Geschwulstforsch; 51(6):493-496 1981

Adjuvant BCG immunotherapy was tested in 114 patients with histologically confirmed malignant melanoma. Cases included 98 Stage I and 16 Stage II patients treated over a 5-yr period. All patients were tested for delayed cutaneous hypersensitivity to tuberculin and dinitrochlorobenzene (DNCB) and for blastogenic response of lymphocyte cultures to phytohemagglutinin and DNCB prior to and during treatment. BCG (6 x 10(8) colony forming units) was administered by scarification weekly for 3 mo, then monthly for 2 yr and every 3 mo thereafter for 3-5 yr. Results in BCG-treated patients were compared with a nonrandomized historical control group. Immunological examination showed no stimulation of immune response in Stage I or II cases. Recurrence and survival rates showed significant improvement in Stage I patients (20-30% survival rate), but not in Stage II patients. Results do not indicate BCG as optimum therapy for malignant melanoma, but further research is indicated. (8 Refs)

8. LYMPHOID CELLS INFILTRATING HUMAN PULMONARY TUMORS: EFFECT OF INTRALESIONAL BCG INJECTION.

Niltsuma M, Golub SH, Edelstein R, Holmes EC
(c/o Golub), Univ. California Los Angeles Sch. Medicine, 54-140 CHS, Los Angeles, CA, 90024
JNCI; 67(5):997-1003 1981

Tumor-infiltrating lymphocytes (TIL) and regional lymph node lymphocytes (LNL) were isolated by mechanical disaggregation and density gradient centrifugation from 30 untreated human lung tumors and 12 BCG-injected human lung tumors. Lymphocyte populations were characterized by their ability to form erythrocyte (E)-rosettes, RBC-antibody-complement, and RBC-antibody gamma-rosettes, by their proportion of esterase-staining cells, and by their responses in mixed lymphocyte culture (MLC), cell-mediated lympholysis (CML), and natural killer (NK) assays. TIL from untreated tumors had low proportions of E-rosetting cells (mean, 27.3%), relatively high proportions of 'null' cells, and poor responses in MLC-CML and NK assays. There were no significant differences between primary lung tumors and lung metastases in rosettes, MLC-CML responses, or NK activity. In contrast, TIL from tumors injected with BCG 14 days before resection had higher proportions of E-rosetting cells (47.8%) and vigorous MLC-CML and NK responses. LNL from 11 patients with untreated tumors had higher proportions of E-rosetting cells (40.5%) than LNL from 9 patients with BCG-injected tumors (35.0%), and LNL from patients with untreated tumors had higher responses than LNL from treated patients in MLC-CML assays. These results suggest that the BCG injection induced an infiltration of functionally reactive NK and T-cells at the tumor site without an associated increased activity of T-cells from regional lymph nodes. (Author abstract) (32 Refs)

9. COMBINATION CHEMOIMMUNOTHERAPY WITH FAC-BCG FOR METASTATIC BREAST CANCER: THE IMPACT OF CMF MAINTENANCE CHEMOTHERAPY.

Hortobagyi GN, Blumenschein GR, Buzdar AU, Yap HY, Schell FC, Barnes BC, Burgess MA
Medical Breast Service, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
J Surg Oncol; 18(2):163-172 1981

In an attempt to prolong the durations of remission and survival of patients with advanced breast cancer treated with the FAC(5-Fluorouracil, Adriamycin, cyclophosphamide)-BCG protocol, we modified the CMF (cyclophosphamide, methotrexate, 5-Fluorouracil) maintenance combination by increasing the dose of all three drugs and administering them iv. Eighty-five evaluable patients treated with this new regimen were compared with a recent historical control group of 105 evaluable patients treated with FAC-BCG and a lower-dose, oral CMF maintenance program. The overall (70% and 76%) and complete (16% and 19%) response rates were identical in these two groups. The median times to progression for all patients entered were similar too (13 mo for both groups). The durations of response were 17 mo (PO-CMF) and 14 mo (IV-

CMF), not significantly different ($p = 0.16$). The durations of survival of the two treated groups were also very similar. After the administration of intensive FAC induction therapy, a high-dose, iv CMF maintenance program appears no better than a low-dose oral regimen. Other drug combinations consisting entirely of drugs not used in the induction regimen might be better choices for maintenance treatment. (Author abstract) (16 Refs)

10. A COMPARISON OF THE TOXICITY OF TWO FORMULATIONS OF CORYNEBACTERIUM PARVUM IN A DOUBLE-BLIND CROSSOVER TRIAL IN PATIENTS WITH BRONCHOGENIC CARCINOMA.

Mitcheson HD, Priestman TJ
(c/o Priestman) Wellcome Res. Lab., Beckenham, Kent, England
Clin Oncol; 7(3):179-182 1981

The clinical toxicities of two preparations (A, formalin-killed wet-filled; B, heat-killed freeze-dried) of Corynebacterium parvum were compared in 10 patients (9 men, 1 woman; 52-74 yr old) receiving the organism as part of a planned course of treatment for inoperable bronchogenic carcinoma. Four patients completed the treatment, two were withdrawn due to disease progression to a preterminal state, and four, who found the C parvum toxicity to be unacceptable, declined completion of the trial. In all, 13 infusions of A and 12 of B were administered. Malaise, rigors, and fever were observed following each infusion. All patients showed a rise in blood pressure during infusion followed several hr later by transient hypotension. Four patients became shocked and required intensive medical support with fluid replacement and steroids. In each case these severe hypotensive episodes followed administration of the A form. Other side effects included vomiting, diarrhea, influenza-like syndrome, and naso-labial herpes simplex sores. When the trial was completed, it was found that 9/11 courses classified as 'less toxic' had used the B form of C parvum, whereas 11/14 courses considered 'more toxic' had used the A form. The median Hb remained unchanged after the C parvum administration, while WBC count increased and the platelet count decreased. Results indicated that use of the B form of C parvum decreases C parvum-associated side effects. (5 Refs)

11. PHASE I STUDY OF SYSTEMIC LYMPHOKINE (LK) ADMINISTRATION IN ADVANCED CANCER PATIENTS (MEETING ABSTRACT).

Gouveia J, Ribaud P, Goutner A, Mathe G
Hopital Paul-Brousse, 94804 Villejuif Cedex, France
Third International Symposium on Human Lymphokines, October 15-17, 1981, Dallas Texas Wadley Institutes of Molecular Medicine; 1981

An LK preparation obtained from a human lymphoblastoid cell line and deprived of Interferon (Organon) was injected IV into 11 advanced cancer patients (pts). For the first 7 pts daily dosage escalation was planned as follows: 20, 20, 30, 30, 50, 75, 100, 150, 200, 300, 400 and 500 gamma LK. A limiting toxicity consisting of high blood pressure, fever, chills and dyspnea occurred in 3 pts receiving 50 gamma LK (2 pts) and 75 gamma LK (1 pt). This toxicity was seen 60 to 90 min after the LK administration and was rapidly reversed by prednisone. Four additional pts were designated to receive daily 20 then 100 gamma of a control protein, then 20, 50, 100, 200, 300, 500, 700, 900, 1100, 1400, 1700 and 2000 gamma LK. The same limiting toxicity occurred in 1 pt at the dose of 300 gamma. Otherwise almost all pts experienced daily moderate and transient fever and/or chills. No correlation was found between the intensity of reaction to IV LK and that of prior id LK. No other side effects were seen. No antitumoral effect was detected. Four pts were submitted to an immunological study, the results of which are reported elsewhere. As no dose-related toxicity was seen, futher clinical studies will include higher doses given in a daily escalating schedule. (no Refs)

12. SYSTEMIC LYMPHOKINE TREATMENT OF SELECTED CANCER PATIENTS (MEETING ABSTRACT).

Southcott BM, Dumonde DC, Pulley MS, Van Vliet E, Den Hollander F, Schuurs A

Department of Radiotherapy, Charing Cross Hospital, London, England

Third International Symposium on Human Lymphokines, October 15-17, 1981, Dallas Texas Wadley Institutes of Molecular Medicine; 1981

Lymphoid cell line lymphokine (LCL-LK), prepared from the supernatant of cultured RPMI 1788 cells, was given iv to 20 patients with advanced cancer under circumstances of close clinical supervision and informed consent. All patients had failed to respond to other treatment modalities. The objective and subjective acute clinical responses (ie temperature rise, rigors, and occasional nausea and vomiting) were made a basis for assessing the maximal tolerated dose. Patients were then maintained on this dose thrice weekly in the shorter term and weekly in the longer term; three patients received treatment for more than 17 mo. There was no evidence of long-term toxicity attributable to the lymphokine. In view of this lack of toxicity, protocols have now been devised for assessment of the effect of systemic lymphokine treatment upon immunological status, with particular reference to lymphocyte function. Initial evidence suggests that lymphokines may have a role in the treatment of cancer, in particular, in association with other forms of therapy. (no Refs)

13. HORMONAL, HAEMATOLOGICAL AND ACUTE PHASE PROTEIN RESPONSES OF ADVANCED CANCER PATIENTS TO THE INTRAVENOUS INJECTION OF LYMPHOID CELL LYMPHOKINE (LCL-LK) (MEETING ABSTRACT).

Pulley MS, Dumonde D, Carter G, Muller B, Fleck A, Southcott B, Den Hollander F

Department of Immunology, St. Thomas Hospital, London, England

Third International Symposium on Human Lymphokines, October 15-17, 1981, Dallas Texas Wadley Institutes of Molecular Medicine; 1981

LCL-LK was given iv to patients with advanced cancer. In addition to the pyrexial response, a neutrophil leukocytosis occurred with a peak at 2-4 hr after injection, and accompanied by a transient lymphopenia with a trough at around 4 hr. This was associated with a rise in serum cortisol, maximal at 2-4 hr. There was no alteration in growth hormone, prolactin or blood glucose levels. The effect of lymphokine on thyroid and sex hormone levels was also investigated. Levels of acute phase proteins were found to increase: C-reactive protein reached a max between 12-24 hr and alpha 1 acid glycoprotein levels peaked later. These effects of lymphokines differ from stress responses as well as from the known response to interferon. The results suggest tht lymphokines have selective effects upon endocrinological and other biochemical parameters as well as upon the compartmentation of WBC. (no Refs)

14. A HISTOLOGICAL STUDY OF INTRADERMAL AND INTRALESIONAL INJECTION OF HUMAN LYMPHOID CELL LINE LYMPHOKINE (LCL-LK) IN PATIENTS WITH ADVANCED CANCER (MEETING ABSTRACT).

Dumonde DC, Paradinas F, Pulley M, Southcott B, O'Connell D, Robinson M, Den Hollander F
St. Thomas Hospital, London SE1, England
Third International Symposium on Human Lymphokines, October 15-17, 1981, Dallas Texas Wadley Institutes of Molecular Medicine; 1981

LCL-LK prepared from the cell line RPMI 1788 was injected into uninvolved skin of tumor-bearing patients. Excision biopsies were taken from 30 min to 72 hr, and for comparison, similar biopsies were taken of tuberculin skin reaction. One-6 injections of LCL-LK were given into breast carcinoma nodules and excision biopsies were done 1-7 days later. The lymphokine skin reaction superimposed an early polymorph infiltration upon a tuberculin-type mononuclear cell exudation. Intralesional injection of LCL-LK resulted in tumor cell necrosis accompanied by lymphocyte and macrophage infiltration; some necrotic tumor cells appeared to be in contact with invading mononuclear cells. This study supports the view that lymphokines are mediators of delayed hypersensitivity in man and extends evidence that intralesional injection of lymphokines results in local tumor regression. (no Refs)

15. PHASE I CLINICAL STUDIES WITH HUMAN LYMPHOBLASTOID LYMPHOKINES (MEETING ABSTRACT).

Rodes ND, McEntire JE, Dunn PA, Oxenhandler RW, Perez-Mesa C, Papermaster BW
Cancer Research Center, Columbia, MO
Third International Symposium on Human Lymphokines, October 15-17, 1981, Dallas Texas Wadley Institutes of Molecular Medicine; 1981

Two lymphoblastoid lymphokine preparations were studied in cancer patients. In the first group, 19 patients were studied with increasing doses of lymphokine preparations administered sc. Patients with stage III and IV metastatic cancer were placed on protocol and blood was obtained for hemograms, basic chemistries, and cellular immune function studies. Dose ranges from 3 to 3,000 units were tested in a predominantly single dose study. No signs of clinical toxicity or disturbance in blood chemistry values were noted following lymphokine injections. Studies with 15 additional patients having basal cell carcinoma of the skin were carried out with an acid soluble fraction. No toxicity was observed with this fraction. A one yr follow-up of basal cell studies on tumor responses will be reported. (no Refs)

SYNTHETIC IMMUNOTHERAPEUTIC AGENTS

16. INTERFERON-INDUCING AND ANTIVIRAL ACTIVITY OF LEVAMISOLE.

Ershov FI, Grigorian SS, Kremerman IB, Nikolaeva OV
D. I. Ivanovskii Inst. Virology, Moscow, USSR
Antibiotiki; 26(8):617-620 1981

The interferon (IF)-inducing activity of levamisole (LM) was studied in random-bred-albino mice. The peak of IF (320-640 IU/ml) in the blood plasma was recorded 4-6 hr after LM administration (100 mg/kg, po). LM provided a 35-40% protection against tick-borne encephalitis. LM was ineffective against influenza virus. (13 Refs) (In RUS)

17. THE INFLUENCE OF ICRF-159 AND LEVAMISOLE ON THE INCIDENCE OF METASTASES FOLLOWING LOCAL IRRADIATION OF A SOLID TUMOR.

Baker D, Constable W, Elkon D, Rinehart L

Div. Radiation Oncology, Dept. Radiology, Univ. Virginia Medical Center, Charlottesville, VA, 22908

Cancer; 48(10):2179-2183 1981

Courses of irradiation consisting of 6,000 rad in 10 equal fractions over 12 days delivered to KHT sarcomas in mice controlled 55% of the local tumors but 83% of the mice died from metastases. Three strategies to reduce the risk of metastatic spread were tested. The fractionation scheme was changed to deliver the same total dose using a large initial fraction followed by seven equal portions with the same overall time. ICRF-159 was used with the intention of partially synchronizing the tumor growth fraction in a radiosensitive state of the growth cycle and of promoting normalization of the tumor vasculature. Levamisole was used to stimulate the immune system. The combination of ICRF-159 with the eight-fraction radiation course proved to be effective for both increasing local control and decreasing the incidence of metastases. The addition of levamisole did not improve the results obtained with a combination of ICRF-159 and irradiation. (Author abstract) (32 Refs)

18. IMMUNOMODULATORY, ANTITUMOR AND ANTIVIRAL EFFECTS OF CP-46,665 AND ITS ANALOGS (MEETING ABSTRACT).

Kraska AR, Pollack VA, Hoffman WW, Wolff JS, Hemsworth GR

Central Research, Pfizer Inc., Groton, CT, 06340

Program and Abstracts of the 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, November 4-6, 1981, Chicago, Illinois American Society for Microbiology; :A329 1981

CP-46,665, 4-aminomethyl-1-[2,3-(di-n-decyloxy)-n-propyl]-4 phenylpiperidine dihydrochloride, is a novel, low mol wt, synthetic lipoidal amine exhibiting antitumor activity in mice. It is derived from a series of 4-aminomethyl-4-phenylpiperidines, which vary in their ability to induce interferon, activate macrophages and produce antitumor effects. These piperidine analogs have been studied in vitro and in vivo for their effects on enhancing macrophage (peritoneal and alveolar) cytotoxicity, and this property has been correlated with their antitumor effects. CP-46,665, the most potent membrane of the series, is an effective activator of peritoneal macrophages after ip administration (0.6 mg/kg) in mice. While CP-46,665 does not appear to induce interferon, subtle structural changes provide compounds that both induce interferon and activate marcophages. The most effective interferon inducers protect mice from a lethal encephalomyocarditis virus challenge and the most effective macrophage activators prolong the survival of sarcoma 180J bearing mice. In a B-16 metastatic melanoma model in mice, CP-46,665 and several of its analogs reduce or prevent pulmonary metastases. Because of the activity profile of these lipoidal amines, they are of interest as synthetic prototypes for cancer immunotherapy. (no Refs)

19. 2-CYANOETHYL UREA AND ITS DERIVATIVES AS POTENTIAL IMMUNOSTIMULANTS IN EXPERIMENTAL CANCER THERAPY.

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Arch Geschwulstforsch; 51(6):485-491 1981

The immunostimulant properties of 2-cyanoethyl urea (CEU) were studied in randomly bred male Wistar rats and ICR mice. Rats received CEU (varying doses) or ifosfamide (IF: 150 mg/kg body wt) iv. Mice were given CEU or IF po, iv, or ip. A single injection of 165 mg CEU/kg body wt increased WBC counts in rats up to 160% within 10 days, followed by a decline that was still above normal levels after 30 days. A single dose of IF produced a decrease in WBC count within 10 days which returned to normal after approx 20 days. CEU given in five doses of 165 mg/kg body wt significantly reduced the effects of IF and increased WBC count to 210% of initial values. Lymphocyte counts were raised 529%. A series of 20 CEU injections (165 mg/kg body wt) permanently raised WBC count 186% and lymphocyte count 560%. Plaque-forming cells in mouse spleens showed decreases following iv or po administration of CEU and in controls. Values for CEU-treated mice were always approx twice those for controls. As measured by footpad swelling CEU raised delayed type hypersensitivity in mice challenged with dinitrochlorobenzene. CEU showed low toxicity even at high doses. Results suggest the usefulness of CEU in clinical trials to improve immune response in human cancer patients. (19 Refs)

20. REGRESSION OF HEAD AND NECK CARCINOMA WITH A PROSTAGLANDIN-SYNTHESIS INHIBITOR.

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Dept. Otolaryngology and Maxillofacial Surgery, Univ. Iowa Hosp., Iowa City, IA, 52242

Arch Otolaryngol; 107(11):658-663 1981

The in vivo administration of a prostaglandin-synthetase inhibitor inhibited or reduced tumor growth in cancer patients and experimental animals. Indomethacin, a prostaglandin-synthetase inhibitor and nonsteroidal anti-inflammatory agent commonly used in the management of arthritic patients, acted as an immune adjuvant by decreasing the production of prostaglandins. Seven cases demonstrated that indomethacin taken in the usually recommended dosages causes regression and stabilization of head and neck cancer. The following factors were also considered in this study: prostaglandin production, a survey of other reports of solid neoplasm response to prostaglandin-synthetase inhibitor administration, drug toxicity, irradiation therapy and metastases, the need for tumor biopsy, and the role that reduction in inflammation plays in tumor shrinkage. (Author abstract) (27 Refs)

INTERFERON

21. LYSIS OF HUMAN B-LYMPHOCYTE-DERIVED LYMPHOMA/LEUKEMIA CELLS OF ESTABLISHED CELL LINES BY INTERFERON-ACTIVATED NATURAL KILLER (NK) CELLS.

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Int J Cancer; 28(4):459-468 1981

Cultured cell lines derived from malignant Epstein-Barr virus (EBV)-negative B cells, and representative of the more common types of naturally occurring non-Hodgkin lymphomas and related leukemias, were found to be sensitive to lysis by human natural killer (NK) cells. The observed lysis of such cell lines was mediated by a population of interferon-augmentable, FcR-positive, non-adherent lymphoid cells, which were also able to kill the 'standard' NK targets K562 and Molt-4. When the NK susceptibility of the neoplastic, EBV-negative B cells was compared to that of diploid, EBV-carrying, non-neoplastic B lymphoblastoid cell lines (BLCLs) and of the 'standard' NK target K562, several distinct patterns were observed. The killing of the neoplastic B cell lines was significantly less than that of K562, but significantly greater than that of the EBV-derived BLCLs of non-neoplastic origin. An additional finding was a similar NK susceptibility profile for the neoplastic, true histiocytic cell line U-937 (ie, K562 greater than U937 greater than BLCLs). Furthermore, all cell lines, with the exception of the BLCLs, could effectively compete for the observed killing in cold target inhibition assays. The implications of these findings are discussed in relation to both neoplastic and non-neoplastic targets of NK lysis. (Author abstract) (49 Refs)

22. EFFECTS OF HUMAN LYMPHOBLASTOID INTERFERON ON CULTURED BREAST CANCER CELLS.

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Int J Cancer; 28(4):447-453 1981

The effect of human interferon on growth and fibronectin production in a range of cultured breast cancer cell lines has been investigated. The cell lines differ in their sensitivity to interferon's growth-inhibitory effect as determined from growth curves, but the degree of sensitivity varies according to the method of assay. When growth was measured in cultures seeded with fairly large numbers of cells, five out of seven lines examined showed a reduction of 50% or more in the number of attached cells after treatment for 8 days with 1,000 units/ml of interferon. Growth of the two cell lines least affected by interferon treatment in dense culture could, however, be markedly inhibited under conditions of clonal growth in agar or when sparsely seeded on plastic and this was due to inhibition of initiation of growt h. In some breast epithelial lines, where the number of attached cells was regulated in part by cell shedding, it was found that interferon not only inhibited cell proliferation, but also increased cell shedding. To determine if interferon increased cell shedding by affecting fibronectin production, the total and cell associated fibronectin was estimated in control and interferon-treated cultures. Four of 10 cell lines examined produced detectable amounts of fibronectin, and in only 1 of these lines, Hs578T derived from a carcinosarcoma, was the production and retention of fibronectin inhibited by interferon treatment. In those breast carcinoma lines which produced detectable amounts of fibronectin, the level of production and retention of the protein, expressed as a proportion of the total protein, did not change after interferon treatment, but showed an increase if expressed on a per cell basis. This is explained by the fact that the interferon-treated cells showed an increase in cell vol. (Author abstract) (36 Refs)

23. LYMPHOKINE PRODUCTION BY PHA-STIMULATED HUMAN LYMPHOCYTES IS ENHANCED BY INTERFERON.

Blomgren H, Einhorn S
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Int Arch Allergy Appl Immunol; 66(2):173-178 1981

Human interferon (IFN) was examined for its capacity to modify the phytohemagglutinin (PHA)-triggered release of mitogenic factors (MF) from human lymphocytes in vitro. It was observed that the presence of partially purified leukocyte IFN (IFN-alpha) during the PHA pulsing of the lymphocytes increased their subsequent release of factors which were mitogenic for fractionated T cells. A similar effect was also observed when lymphocytes were exposed to IFN-alpha prior to PHA pulsing. The possibility that substances in the IFN preparations other than IFN are responsible for the above effect is ruled out by the finding that a pure fibroblast IFN (IFN-beta) preparation also augmented the MF release by PHA-pulsed lymphocytes. (Author abstract) (22 Refs)

24. INTERFERON INCREASES THE ABUNDANCE OF SUBMEMBRANOUS MICROFILAMENTS IN HELA-S3 CELLS IN SUSPENSION CULTURE.

Wang E, Pfeffer LM, Tamm I
Rockefeller Univ., New York, NY, 10021
Proc Natl Acad Sci USA; 78(10):6281-6285 1981

Human beta(fibroblast) interferon inhibits the proliferation of human HeLa-S3 carcinoma cells in suspension culture. Accompanying this effect, the lateral mobility of cell surface receptors for concanavalin A is decreased and the rigidity of the plasma membrane lipid bilayer is increased. The present findings show a marked increase in the number of polymerized actin-containing microfilaments 3 days after treatment of HeLa-S3 cells with beta-interferon (640 units/ml). The cortical region of the treated enlarged cells contains a thick and dense meshwork of 40-70 A microfilaments. The actin nature of the filaments was verified by their ability to bind heavy meromyosin. These results support the concept that beta-interferon induces a coordinated response in the plasma membrane and the underlying microfilaments in both tumor and normal cells. (Author abstract) (35 Refs)

25. ANTI-PROLIFERATIVE ACTIVITIES OF HUMAN INTERFERONS (MEETING ABSTRACT).

Kaplan NO, Slimmer S
Department of Chemistry and Cancer Center, University of California at San Diego, La Jolla, CA, 92093
Thirteenth Miami Winter Symposium: Cellular Responses to Molecular Modulators, January 12-16, 1981, Miami, Florida. University of Miami 112 pp., 1981.

Interferons have been reported to have both anti-viral and anti-proliferative actions. Most of these studies with human interferons have been carried out with unpurified preparations. Recently there have been major developments in the purification of human interferons. As a result of obtaining purified material, it has been found that there are a number of interferons existing which have different amino acid sequences. We have compared the anti-proliferative activities of a number of interferons with their anti-viral activities. It has been found that crude human fibroblastic interferon is more cytotoxic than crude leukocytic interferon. Some highly purified leukocytic interferons have been found to have little or no anti-growth activity whereas they have a high specific activity for the anti-viral effect. On the other hand, other fractions have been isolated which contain both anti-proliferative and anti-viral activities. Pure human fibroblastic interferon is highly active with respect to its anti-growth potential. As a result of these studies, we have preliminarily concluded that there may be three types of interferon: (1) a form which has high anti-viral activity but little or no anti-growth activity, (2) a form which has anti-viral activity as well as cytostatic effect on cells, (3) a form having both cytotoxic and anti-viral activities. Our studies were done with a cloned cell line of a human astrocytoma. This cell line seems to be most sensitive to the interferons. We are correlating the differences in sequence with the difference in activity of the various interferons. It appears to us that close scrutiny must be made of the different interferons to be certain whether they have cytotoxic action. We are now conducting studies to determine whether the assay system we are using reflects the chemotherapeutic effects observed in human patients. (no Refs)

26. IN VITRO INHIBITORY EFFECT OF INTERFERON ON DNA SYNTHESIS OF BREAST CANCER CELLS AND RELATIONSHIP TO STEROID RECEPTORS (MEETING ABSTRACT).

Jakesz R, Kerjaschki D, Kolb R, Reiner G, Spona J, Swetly P
University of Vienna, A-1090 Vienna 9, Austria
Eur Surg Res; 13(1):31 1981

For selecting patients for postoperative interferon treatment we carried out the following in vitro study. From 22 patients with primary or recurrent breast cancer, fresh tumor tissue was obtained. Tissue cultures were prepared from mouse bone marrow cells according to the method of Dexter et al, and used as a feeder layer for cultivation of breast cancer cells in a humified atmosphere. At least 48 hr after incubation, confluent tumor cell colonies could be determined and the cells could be differentiated as epithelial using electron microscopy. For determining the influence of interferon DNA synthesis 3H-thymidine uptake was measured after incubation of breast cancer cells with interferon or without for control. Human lymphoblast interferon (HLI) was obtained from Namalwa cells after induction by Sendai virus. Human fibroblast interferon (HFI) was induced in human fibroblasts by Poly I:C and purified by controlled pore glass chromatography. Ten and 100 U/ml interferon were used. Forty-eight hr after incubation with interferon 3H-thymidine was measured. (1) An optimal reduction of DNA synthesis could be achieved in 32% with 100 U/HFI and in 62% with the same dose of HLI. (2) Using only 10 U interferon, only suboptimal reductions were seen. (3) 22% of ER + culture cells show a marked reduction of DNA synthesis compared with 50% ER cells. These results indicate that 100 U HLI is more effective than the same dose of HFI. The higher response rate of cells or ER tumors could be an argument for selecting ER patients for interferon therapy. (3 Refs)

27. ANTIRETROVIRAL ACTION OF INTERFERON (MEETING ABSTRACT).

Naso R, Wu Y, Arlinghaus R, Edbauer C
Department of Tumor Virology, University of Texas System Cancer Center, Houston, TX
Thirteenth Miami Winter Symposium: Cellular Responses to Molecular Modulators, January 12-16, 1981, Miami, Florida. University of Miami 112 pp., 1981.

Mouse fibroblast interferon (IF) inhibited the release of Rauscher leukemia virus from chronically infected NIH Swiss mouse embryo cells by 90-95% at 10 units/ml. The antiretroviral effect was prevented by preincubation of the IF with trypsin or with antiserum of IF or by incubation of the cells with Actinomycin D IF treatment did not alter the synthesis of any known viral precursor protein; nor did it alter the intracellular cleavage of those precursors into the proteins of mature virions. Furthermore, the viral proteins characteristic of the virus released from IF-treated cells appeared normal with the exception of an extremely small amount of fucosylated glycoprotein precursor, gPr93env, which was incorporated into the envelope of the virus. This precursor-like protein, however, was present in comparable amounts in both control and IF-treated cells. We found, using a radioimmuno-precipitation assay to measure levels of precursor polyproteins in newly infected cells, that virus released by IF-treate d cells was nearly as infectious as virus released from normal cells. The above results suggest that IF induces in cells an antiretroviral effect without an apparent alteration in any viral component. It is also suggested that IF induces alterations in cellular structures (eg membranes) so as to alter functions (eg membrane fluidity) which are necessary for the recruitment of viral proteins and/or the clearing of cell proteins at virus assembly sites in the cell membrane. We have not, however, observed any alteration in cell microtubule or microfilament structure (at concentrations of interferon up to 300 units/ml) which would effect the presumed change in membrane fluidity; nor have we observed, at this point in time, any unusual partitioning of viral proteins between cytoplasmic and membrane structures during IF treatment. It remains to be determined whether IF treated of cells induces the synthesis of integral membrane proteins which, when inserted into the cell membranes, alter membrane fluidity and, therefore, virus assembly. (no Refs)

28. PURIFICATION OF THE HUMAN INTERFERONS, CLONING OF THE SEQUENCES, AND EXPRESSION IN BACTERIAL RECOMBINANTS (MEETING ABSTRACT).

Pestka S, McCandliss R, Maeda S, Levy WP, Familletti PC, Hobbs DS, Moschera J, Stein S
Roche Institute of Molecular Biology, Nutley, NJ, 07110
Thirteenth Miami Winter Symposium: Cellular Responses to Molecular Modulators, January 12-16, 1981, Miami, Florida. University of Miami 112 pp., 1981.

New techniques for purifying proteins by high performance liquid chromatography were used to purify the human interferons to homogeneity. By these techniques, many species of human WBC interferon were purified and the amino acid sequence of one largely determined. The individual species exhibit characteristic structures and vary in their biological activities. Some species exhibit relatively high antiviral activities, whereas other species exhibit greater antigrowth activity. Accordingly, we conclude that human WBC interferon consists of a family of closely related and homologous proteins, a conclusion confirmed by the isolation of multiple distinct complementary DNA (cDNA) and genomic recombinants containing the human interferon sequences. The ability to translate interferon messenger RNA into a biologically active protein allowed its isolation, partial purification, and use as a template for synthesizing cDNA. The cDNA was used to prepare recombinants containing the human interferon nucleic acid sequences. Definitive identification was confirmed by correspondence of the nucleotide sequence with our amino acid sequences of human WBC interferon. With the expression of human WBC interferon in bacteria, a number of studies have been initiated with this material. Restriction analysis and sequencing of interferon-related DNAs isolated from a h uman gene library indicate that the diversity of the WBC interferons appears to be represented by multiple individual genomic equivalents. The structural modulation of these biological activities has immense significance for understanding the natural role of the interferon. as well as for refining and developing their ultimate therapeutic potential. (9 Refs)

29. DNA SEQUENCE OF A MAJOR HUMAN LEUKOCYTE INTERFERON GENE.

Lawn RM, Gross M, Houck CM, Franke AE, Gray PV, Goeddel DV
Dept. Molecular Biology, Genentech, Inc., 460 Point San Bruno Blvd., South San Francisco, CA, 94080
Proc Natl Acad Sci USA; 78(9,part2):5435-5439 1981

The gene for human leukocyte interferon alpha2 (designated either LeIF or HuIFN-alpha2) has been isolated from a human genome library. The DNA sequence of this gene demonstrates that it lacks introns. The 3' noncoding sequences of the IFN-alpha2 gene correspond to two types of IFN-alpha2 cDNA clones we have isolated that have alternate sites of polyadenylylation. A comparison of seven human IFN-alpha sequences shows that they are homologous in the 5' flanking region and contain identical 'TATA box' sequences. The recombinant lambda clone containing the IFN-alpha2 gene also contains two copies of the 'Alu family' repeat sequence. (Author abstract) (38 Refs)

30. AMINO ACID SEQUENCE OF A HUMAN LEUKOCYTE INTERFERON.

Levy WP, Rubinstein M, Shively J, Del Valle U, Lai CY, Moschera J, Brink L, Gerber L, Stein S, Pestka S
Roche Inst. Molecular Biology, Nutley, NJ, 07110
Proc Natl Acad Sci USA; 78(10):6186-6190 1981

The primary structures of three major species of human leukocyte interferon differ from the structure predicted from the DNA sequence of recombinants containing leukocyte interferon-coding regions. Compared to the recombinant interferon produced in bacteria, three of the purified natural proteins isolated from WBC lack the 10 COOH-terminal amino acids suggested by the DNA sequence. (Author abstract) (36 Refs)

31. FURTHER HETEROGENEITY OF HUMAN ALPHA INTERFERON MRNA SPECIES.

Sehgal PB, Sagar AD, Braude IA
Rockefeller Univ., New York, NY, 10021
Science; 214(4522):803-805 1981

Translationally active (in Xenopus oocytes) human alpha interferon (IFN) messenger RNA's (mRNA's) derived from Sendai virus-induced WBC cultures display a bimodal distribution of RNA lengths on electrophoresis through agarose-CH3HgOH gels. The major population (alphas) consists of mRNA of length 0.7 to 1.4 kilobases, while the minor population (alphaL) consists of RNA of length 1.6 to 3.5 kilobases. Induction of human WBC in the presence of 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole (DRB; 100 micromolar) appears to inhibit the accumulation of IFN-alphas and to enhance that of IFN-alphaL mRNA's (av length about 1.8 kilobases in preparations from DRB-treated cells). Interferons derived from the alphas mRNA's represent the group of previously recognized alpha interferons while the alphaL interferons are distinguishable from this group by their lower heterospecific activity on bovine cells compared to human cells, their apparent slower mobility in sodium dodecyl sulfate-polyacrylamide gels, and their apparent heteroclitic response toward an antiserum to IFN-alpha. (Author abstract) (15 Refs)

32. EXPRESSION OF A HUMAN GENE FOR INTERFERON IN YEAST.

Hitzeman RA, Hagie FE, Levine HL, Goeddel DV, Ammerer G, Hall BD
Dept. Molecular Biology, Genentech Inc., 460 Point San Bruno Blvd., San Francisco, CA, 94080
Nature; 293(5835):717-722 1981

A DNA sequence coding for mature human leukocyte interferon D (LeIF-D) was linked with DNA fragments of the 5'-flanking sequences of the Saccharomyces cerevisiae (yeast) alcohol dehydrogenase I gene in a plasmid capable of autonomous replication and selection in both yeast and Escherichia coli. Yeast cells transformed by these plasmids synthesize up to 1 x 10(6) molecules of biologically active LeIF-D per cell. (Author abstract) (30 Refs)

33. STRUCTURE OF A CHROMOSOMAL GENE FOR HUMAN INTERFERON BETA.

Ohno S, Taniguchi T
Dept. Biochemistry, Cancer Inst., Japanese Foundation for Cancer Research, Toshima-ku, Tokyo 170, Japan
Proc Natl Acad Sci USA; 78(9,part2):5305-5309 1981

We have cloned and analyzed a chromosomal DNA segment containing the human interferon beta1 gene from a human gene library. The nucleotide sequence of the protein-coding and the noncoding regions of the chromosomal gene was identical to the cDNA sequence reported previously. In the region upstream from the putative transcription initiation site, significant nucleotide sequence homology was observed between interferon beta1 and alpha1 genes. This region thus may play a role in expression of the interferon genes. From the sequence data and the result of nuclease S1 mapping experiments, we conclude that, like the interferon alpha1 gene, the interferon beta1 gene is devoid of intervening sequences. (Author abstract) (40 Refs)

34. THE INDUCTION OF AT LEAST TWO DISTINCT TYPES OF INTERFERON IN MOUSE SPLEEN CELL CULTURES BY CORYNEBACTERIUM PARVUM.

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(c/o Johnson) Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Cell Immunol; 64(1):64-72 1981

Stimulation of dissociated C57Bl/6 mouse spleen cells with Corynebacterium parvum resulted in the production of interferon (IFN) activity that was only partially neutralized by separate treatment with anti-L-cell IFN (anti-IFN-alpha/beta) or anti-gamma IFN (anti-IFN-gamma) antisera. Treatment of the IFN preparation simultaneously with the two antisera resulted in complete neutralization of anti viral activity, thus C parvum induced both IFN-alpha/beta and IFN-gamma in spleen cells. The total number of units of antiviral activity in untreated cultures was greater than the sum of the titers of the individual IFNs. This is consistent with the phenomenon of 'potentiation', where mixtures of IFN-alpha/beta and IFN-gamma have been shown to exhibit increased antiviral activity. Kinetic studies showed that IFN-alpha/beta activity in cultures peaked at 12 to 24 hr, while IFN-gamma peaked at 48 to 72 hr. The different IFNs induced by C parvum were separated by gel filtration chromatography, with IFN-alpha/beta exhibiting a mol wt of about 25,000 daltons and IFN-gamma a mol wt of 35,000 to 40,000 daltons. Separation of the spleen cells into plastic-adherent and nonadherent populations showed that nonadherent cells were the major producers of both IFN-alpha/beta and IFN-gamma following stimulation with C parvum. Treatment of spleen cell cultures with monoclonal anti-Thy 1.2 antibody and complement greatly reduced the production of IFN-gamma but had little or no effect on the production of IFN-alpha/beta. These data suggest that T lymphocytes are the producers of IFN-gamma, and that IFN-alpha/beta is produced by a nonadherent, non-T cell. Preliminary data suggest that the IFNs may play a role in C parvum-induced immunosuppression. (Author abstract) (20 Refs)

35. HUMAN INTERFERON PRODUCTION IN TONSIL AND ADENOID TISSUE CULTURES (MEETING ABSTRACT).

Richtsmeier WJ
No affiliation given
Otolaryngol Head Neck Surg; 89(5,section2):130 1981

Our laboratory has isolated high titered human interferons from tonsil and adenoid tissue. We have investigated the production in interferon as a central aspect of the immunologic function of the lymphoid tissues of Waldeyer's ring in an effort to answer some of the questions raised concerning the relationship between tonsillectomy and the reported emergence of lymphoproliferative tumors. We have identified the production of millions of units of interferon per tonsil preparation using Sendai virus as an inducer. Previously reported attempts to induce interferon in tonsil cultures described only low titered interferons (10s of units/ml). All tonsil and adenoid tissues in this study were obtained during routine surgical procedures from otherwise healthy individuals. Results from 30 tonsil and ten adenoid preparations assayed indicate that tissue from younger patients produces more WBC interferon (Hu IFN-alpha) than tissue from older patients. In addition to WBC interferon, immune interferons (Hu IFN-gamma) have been identified when galactose oxidase was used as the inducer. Similar responses are seen in adenoid tissue. Both crude cell suspensions and purified lymphocyte preparations appear to be as efficient at producing interferons as are circulating WBC. An additional benefit from this discovery is the theoretic possibility of making enough interferon from tonsil cultures to treat patients with neoplastic diseases. Tonsillar and adenoidal WBC provide an alternative source of interferon, which can be produced on a local level. (no Refs)

36. THE PATHOGENESIS AND CONTROL OF INTERFERON-INDUCED PYREXIA (MEETING ABSTRACT).

Priestman TJ, Lucken R
Wellcome Research Laboratories, Beckenham, Kent, England
Br J Cancer; 43(5):720 1981

Recent papers have reported the use of WBC and fibroblast interferon (IFN) in the treatment of advanced cancer. In all studies pyrexia was seen after initial doses of IFN. The material used in these trials was only 0.1-1% pure, and it has been suggested that fever was caused by non-IFN protein. In a study with lymphoblastoid IFN (HLBI), some 20-50 x purer than IFN used in previous clinical series, pyrexia was initially dose-limiting. The possibility of endotoxin contamination was excluded by negative Limulus lysate assays, chick-embryo toxicity, and rabbit pyrogenicity tests. The clinical and laboratory data indicated that IFN-induced fever was mediated by the release of endogenous pyrogen. A subsequent clinical trial showed that pretreatment with salicylates reduced the degree of fever after HLBI administration. It is concluded that IFN is inherently pyrogenic, causing the release of endogenous pyrogen, and that salicylate therapy will reduce the fever until tolerance to this phenomenon develops 4-5 days after starting IFN treatment. (1 Ref)

INTERFERON INDUCING AGENTS

37. STIMULATION OF HUMAN GAMMA INTERFERON PRODUCTION BY DITERPENE ESTERS.

Yip YK, Pang RH, Oppenheim JD, Nachbar MS, Henriksen D, Zerebeckyj-Eckhardt I, Vilcek J

Dept. Microbiology, New York Univ. Sch. Medicine, New York, NY, 10016

Infect Immun; 34(1):131-139 1981

The diterpene ester 12-O-tetradecanoylphorbol-13-acetate (TPA) and several structurally related compounds were tested for their ability to stimulate interferon (IFN) production in primary cultures of human WBC. In cultures of Ficoll-Hypaque-purified mononuclear cells, TPA treatment alone induced only low levels of IFN, but TPA pretreatment of cells caused significant enhancement of IFN yields produced with phytohemagglutinin or several other T cell mitogens. In cultures of unprocessed cells derived from plateletpheresis residues or buffy coats, TPA treatment alone induced high levels of IFN and costimulation with TPA and phytohemagglutinin produced some further enhancement of IFN production. Phorbol 12,13-dibutyrate was comparable to TPA in its ability to enhance phytohemagglutinin-induced IFN production. Several other phorbol ester analogs were also active, but max stimulation occurred only at higher drug concentrations. Mezerein, a structurally related diterpene ester, was at least as active as TPA in stimulating IFN production in either Ficoll-Hypaque-purified or unprocessed cells. IFN produced after stimulation with TPA or mezerein, singly or in combination with phytohemagglutinin, had several properties characteristic of IFN-gamma, eg, it was largely inactivated by dialysis at pH 2, or after exposure to sodium dodecyl sulfate, whereas it was not neutralized by antibody to IFN-alpha and IFN-beta. The stimulatory effect of diterpene esters has proved helpful in producing IFN-gamma for physicochemical analysis and other studies. (Author abstract) (39 Refs)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

38. IMMUNITY TO TRANSPLANTABLE NITROSOUREA-INDUCED NEUROGENIC TUMORS. I. POTENTIATION OF TUMOR IMMUNITY WITH CORYNEBACTERIUM PARVUM.

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J Neuropathol Exp Neurol; 40(5):526-536 1981

Various injection schedules of C. parvum and tumor cells of the nitrosourea-induced malignant neurinoma, TR-481, were used to induce tumor immunity in syngeneic CDF rats. Although sc injection of the poorly immunogenic TR-481 cells alone or with C parvum caused retardation of growth of 2 x 10(5) TR-481 cells injected 1-3 wk later, no significant difference in tumor size or incidence was obtained, as judged by tumor growth at 8 wk. In contrast, injection of TR-481 with C parvum into C parvum-presensitized rats caused a more significant degree of tumor immunity with complete inhibition of the challenge tumor growth in 17-33% of the animals. Repeated sc injection of gamma-irradiated TR-481 tumor cells mixed with C parvum also proved effective, resulting in absence of tumor growth in 40% of the rats. Tumor immunity was specific, since growth of an unrelated tumor was unaffected. It is suggested that local immunological reactivity to C parvum in the immunizing tumor promotes development of specific tumor immunity. (Author abstract) (37 Refs)

39. COMPARATIVE STUDIES ON ANTIMETASTATIC EFFECTS OF PICIBANIL (OK-432) AND C. PARVUM IN MICE (MEETING ABSTRACT).

Malenica B, Basic I, Milas L

Department of Animal Physiology, Central Institute for Tumors and Allied Diseases, University of, Zagreb Zagreb, Yugoslavia

International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

We have compared the antitumor efficacy of OK-432 and Corynebacterium parvum against lung metastases of syngeneic mammary carcinoma (MCa) and fibrosarcoma (FSa) in CBA mice. Both OK-432 and C parvum (0.25 mg) were injected IV or IP or intrapleurally (IPL) before or after IV tumor cells inoculation. When given before tumor cells, IP OK-432 was ineffective against both FSa and MCa. IV OK-432 was also ineffective against FSa but remarkably reduced the number of MCa metastases. In prophylactic studies, howeve r, both IP and IV C parvum was equally effective. Injected 2 or 7 days after MCa cells, both OK-432 and C parvum markedly and equally reduced the number of metastases. In therapeutic studies IPL OK-432 was effective against MCa but had no effect at all on FSa. In contrast, FSa metastases were sensitive to the effect of C parvum. These results indicate that there is a marked difference in sensitivity of murine tumors to therapeutic properties of OK-432. (no Refs)

40. ACTIVATION AND MECHANISM OF ACTION OF SUPPRESSOR MACROPHAGES.

Lichtenstein A, Murahata R, Terpenning M, Cantrell J, Zighelboim J
Dept. Microbiology and Immunology, Univ. California Sch. Medicine, Los Angeles, CA, 90024
Cell Immunol; 64(1):150-161 1981

Iv administration of Corynebacterium parvum to alloimmunized mice activates splenic suppressor macrophages that effectively curtail primary and secondary generation of cytotoxic T lymphocytes (CTLs) in vitro. CTL generation was significantly inhibited in suppressed primary cultures by Day 3, the earliest time point that activity is first detected in control cultures. Suppressor macrophages had to be present during the first 24-48 hr of culture to effectively curtail the generation of CTLs. However, if suppressor macrophages were reactivated by 48-hr in vitro culture and then added to primary sensitizations that had been initiated 48 hr previously, they were capable of significant suppression. Suppressor cells produced a soluble factor that mediated the inhibition of CTL generation. The production or action of this factor could not be counteracted by indomethacin. (Author abstract) (31 Refs)

MICROBIAL FRACTIONS AND EXTRACTS

41. DOSE, ROUTE, AND TIME DEPENDENCE OF SERUM LYSOZYME AND ANTITUMOR ACTIVITY FOLLOWING ADMINISTRATION OF GLUCAN, CORYNEBACTERIUM PARVUM, PYRAN, OR LIPOPOLYSACCHARIDE TO MICE.

Gorecka-Tisera A, Proctor JW, Yamamura Y, Harnaha J, Meinert K (c/o Proctor), Allegheny Singer Res. Corporation, Radiation Res. Lab., Allegheny General Hosp., Pittsburgh, PA, 15212
JNCI; 67(4):911-915 1981

Following the administration of Di Luzio particulate glucan, Corynebacterium parvum, pyran (maleic anhydride vinyl ether 6), and lipopolysaccharide (Shigella) to inbred C57BL/6J mice, dose, route, and time-dependent studies were undertaken on antitumor activity and serum lysozyme levels to explore the possible relevance of serum lysozyme as a useful index of antitumor activity. Antitumor activity was assessed by measurement of the extent of loss of iv injected ^{125}I-labeled 5-iodo-2'-deoxyuridine-labeled B16 tumor cells. Increases in serum lysozyme levels were dose-, route-, and time-dependent and varied greatly from one agent to another. The peak levels of antitumor activity were similar for all agents but were also critically dose- and time-dependent. Correlations of serum lysozyme levels and antitumor activity were inexact. The doses for peak lysozyme level increases were higher than those for peak antitumor activity. Antitumor activity peaked earlier and lasted longer than serum lysozyme level increases. (Author abstract) (36 Refs)

42. CYTOTOXIC CELLS INDUCED IN TUMOR-BEARING RATS BY A STREPTOCOCCUS PREPARATION (OK-432).

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Dept. Hygienic Chemistry, Pharmaceutical Inst., Tohoku Univ., Aobayama, Sendai 980, Japan
Gan; 72(5):692-699 1981

The characteristics of the cytotoxic cells induced by ip injections of an immunoadjuvant, OK-432 (Picibanil), into ACI/N rats bearing syngeneic bladder cancer, BC47, were examined. The cytostatic activity, but not the cytolytic activity, of peritoneal macrophages was augmented when either normal or cancer-bearing rats were treated with OK-432. In contrast, the plastic non-adherent cells of the peritoneal exudate cells from OK-432-treated cancer-bearing rats, but not lymph node cells or spleen cells, killed all ACI/N rat bladder cancers tested as well as ACI/N rat hepatoma cells and Meth-A mouse sarcoma cells. The plastic nonadherent cells from OK-432-treated normal rats also killed hepatoma cells and Meth-A cells, but not bladder cancer cells. The cytolytic cells that were induced in cancer-bearing rats by OK-432 treatment and showed cytolytic activity specific for bladder cancers were found to be sensitive to anti-rat thymocyte serum and complement, nylon-adherent, and Fc receptor-negative. The cells that showed nonselective cytolytic activity were nylon-adherent and insensitive to anti-rat thymocyte serum and complement. (Author abstract) (24 Refs)

CYTOKINE THERAPY

43. LYMPHOKINE PRODUCTION BY PERIPHERAL BLOOD LEUCOCYTES: QUANTITATION OF T-CELL GROWTH FACTOR ACTIVITY FOR ASSESSMENT OF IMMUNE RESPONSE CAPABILITY.

Warren HS, Pembrey RG
Cancer Res. Unit, Woden Valley Hosp., Post Office Box 11, Woden, ACT 2606, Australia
Aust NZ J Med; 11(5):475-479 1981

Mitogen stimulation of as few of 200,000 human peripheral blood leukocytes (PBL) in 0.2 ml vol produces highly active lymphokine supernatants. The lymphokine activity measured is T-cell growth factor. Under optimum conditions of PHA-P concentration, serum source and concentration, and time, activity is detectable to a dilution of between 1/250 and 1/700 for lymphokine supernatants from PBL of normal donors. Lymphokine supernatants prepared from PBL of donors previously treated with the immunosuppressive regimes of radiotherapy and/or chemotherapy had activities that were between 13% and 66% of normal controls. Lymphokine production as a quantitative measure of immune capability is discussed. (Author abstract) (11 Refs)

44. PURIFICATION AND CHARACTERIZATION OF LYMPHOKINE FRACTIONS ASSOCIATED WITH TUMOR IMMUNOTHERAPEUTIC ACTIVITY (MEETING ABSTRACT).

Papermaster BW, McEntire JE, Smith ME, Gilliland CD, Dunn PA, Rodes ND, Lopatin E
Cancer Research Center, Columbia, MO
Thirteenth Miami Winter Symposium: Cellular Responses to Molecular Modulators, January 12-16, 1981, Miami, Florida. University of Miami 112 pp., 1981.

Our initial experiments were performed with concentrated supernatant preparations of the lymphoblastoid cell line, RPMI 1788, grown in human serum containing medium. Our previously published studies reported that often complete regression of local tumor lesions could be initiated by local injections of crude lymphokine preparations. A recent dose response protocol at Ellis Fischel State Cancer Hospital in Columbia has indicated that NK cell and neutrophil phagocytic capacity are stimulated by appropriate amounts of crude lymphokine preparation injected sc in cancer patients. Fractionation and purification studies with biosynthetic labeling by ^{3}H-amino acids indicated that lymphotoxin and macrophage activating activities were bound to alpha-2 macroglobulin and albumin from culture medium serum. Additional extraction with acids or detergents led to fractions that contained active peptides and albumin. An acid-extracted fraction containing albumin and several additional peptides identified by high performance liquid chromatography has been used successfully in treatment of isolated basal cell carcinomas and mouse lymphoma. This indicated that peptides involved in the acid-extractable fractions are of interest in promoting tumor regression. Further purification by high performance liquid chromatography in 6M guanidine HCl and assay by microphagocytic and NK cell stimulation assays have revealed at least two interesting peptides of less than 10,000 daltons in mol wt. They would thus be expected to bind tenaciously with carrier serum proteins and be undetectable without addition of dissociating detergents or ionic solvents. (no Refs)

45. LYMPHOKINE INDUCED TUMOR REGRESSION AND CURES IN MICE BEARING L1210 ASCITES TUMORS (MEETING ABSTRACT).

Gilliland CD, McEntire JE, Woods WL, Tyrer HW, Papermaster BW
Cancer Research Center, Columbia, MO, 65201
Thirteenth Miami Winter Symposium: Cellular Responses to Molecular Modulators, January 12-16, 1981, Miami, Florida. University of Miami 112 pp., 1981.

Partially purified lymphokine-containing fractions derived from the concentrated supernatants of mouse and human long-term lymphoblastoid cell lines were used to treat DBA/2 mice bearing ascites L1210 tumors. Effective treatment was achieved by substantially reducing tumor load with a single dose of 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (MeCCNu) followed by aggressive lymphokine therapy. Therapeutic effect was noted by 1) increases in median survival time (MST), 2) percent increases in life span (% ILS), and 3) increased resistance to sequentially higher challenge tumor doses of 10(5)-10(7) tumor cells ('cured' animals). Observations were confirmed in two strains of L1210 tumor, After adjustment of proper drug dosage to LD10 levels, cures could be obtained only with combined drug lymphokine therapy. Experiments were designed to study the cells responding to lymphokines and fractions in vivo. Spleen cells from mice injected with single doses of lymphokines demonstrated enhanced cytotoxic activity toward L1210 target cells in in vitro assays. Characterization of these spleen cells by flow cytofluorometry with propidium iodide staining suggested that the responding populations showed an increased DNA turnover and an increased propensity to undergo blastogenesis. Those results suggest that an early reduction of large tumor burden followed by lymphokine administration stimulates non-specific lymphomonocyte cytotoxicity resulting in further tumor destruction to 1 cell and concomitant development of specific lymphocyte-mediated tumor immunity as indicated by resistance to challenge in 'cured' animals. (no Refs)

46. INTERLEUKIN 2 PRODUCTION BY ALLOANTIGEN (H-2) ACTIVATED T CELLS.

Andrus L, Lafferty KJ
Dept. Immunology, John Curtin Sch. Medical Res., Australian Natl. Univ., Post Office Box 334, Canberra City, Australia
Aust J Exp Biol Med Sci; 59(4):413-426 1981

H-2 alloantigen-activated T cells release Interleukin 2 in response to a secondary stimulus by either Concanavalin A or alloantigen. No detectable lymphokine is released in the absence of secondary stimulation and, in the case of alloantigen restimulation, lymphokine release is antigen-specific. Once formed, however, the lymphokine shows no antigen specificity in its action. Like the precursor of the cytotoxic T cell, the precursor of the Interleukin 2-producing T cell requires two signals for its activation; alloantigen and a source of costimulator activity. Once activated, T cells will release lymphokine in response to alloantigen alone. (Author abstract) (18 Refs)

47. PREVENTION OF THE IN VITRO MYELOSUPPRESSIVE EFFECTS OF DEXAMETHASONE BY HUMAN INTERLEUKIN 1 (IL-1) (MEETING ABSTRACT).

Mishell RI, Lee DA, Lachman LB
Department of Microbiology and Immunology, University of California, Berkeley, CA
Third International Symposium on Human Lymphokines, October 15-17, 1981, Dallas Texas Wadley Institutes of Molecular Medicine; 1981

Dexamethasone (10(-8) M) inhibits the formation of granulocyte/macrophage colonies by murine bone marrow cells cultured with colony stimulating factors in semisolid agar. Human IL-1, purified from the supernates of cells from a patient with acute monocytic leukemia protects colony formation from inhibition by steroids. Since IL-1 is normally produced in response to bacterial components that are active as immunological adjuvants and to endogenous mediators of inflammation such as T cell lymphokines, the effects of IL-1 on granulocyte/macrophage precursors may represent an important pathway for maintaining myeloproliferative reactions during the stress of acute bacterial infections. Glucocorticosteroids also inhibit erythropoiesis. Experiments currently being conducted on the effects of IL-1 on erythropoiesis will also be discussed. (no Refs)

48. TUMOR-INHIBITORY AND IMMUNOREGULATORY CYTOKINES CARRIED BY ALPHA2-MACROGLOBULINS OF MICE (MEETING ABSTRACT).

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Department of Microbiology and Immunology, Northeastern Ohio Universities College of Medicine, Rootstown, OH, 44272
Thirteenth Miami Winter Symposium: Cellular Responses to Molecular Modulators, January 12-16, 1981, Miami, Florida. University of Miami 112 pp., 1981.

Homogeneous murine alpha-2-macroglobulins (AMG) isolated from the normal plasma (N-AMG) and cell-free ascitic fluid of a mouse ovarian tumor (T-AMG) have been shown to possess tumor-inhibitory (TI), immunosuppressive (ISP), immunoenhancing (IEN) as well as protease-binding (PB) activities. The TI and ISP activities were stable to heat (57C, 60 min), acid (pH3), and methylamine-treatment, whereas the PB activity was inactivated by similar treatment. The potent ISP activity could be completely removed from AMG by dialysis and recovered in the dialysate. The IEN activity, on the other hand, was non-dialyzable and is stable to acid (pH3) treatment. The TI activity could be partially dissociated from AMG by acid (pH3) dialysis and was shown not to affect the PHA-induced lymphocyte transformation reaction. It appeared to be anti-genically related to the F1-protein which is always carried by N-AMG and T-AMG. Although the isolated F1-protein itself has an amino acid composition similar to that of a human skin cytotoxic and chemotactic proteinase, F1 is clearly different from the conventional proteases in many of its biological and physico-chemical properties. We conclude from these studies that many of the observed activities associated with alpha-2-macroglobulins may result from the activities of cytokines carried by these proteins and that AMG itself does not inhibit tumor cell growth or affect lymphocyte transformation reactions simply by virtue of its protease-binding activity. (1 Ref)

ACTIVE SPECIFIC IMMUNIZATION

49. IMMUNOPROPHYLAXIS OF TRANSPLANTABLE METHYLCHOLANTHRENE-INDUCED MURINE FIBROSARCOMAS BY IMMUNIZATION WITH EMBRYO CELLS EXPRESSING ENDOGENOUS MURINE LEUKEMIA VIRUS ANTIGENS.

Zbar B, Manohar V, Sugimoto T, Ashley MP, Kato Y, Rappaport P
Lab. Immunobiology, NCI, NIH, Bethesda, MD, 20205
Cancer Res; 41(11,part1):4499-4507 1981

We investigated the nature of a common tumor rejection antigen(s) in chemically induced murine fibrosarcomas. Two methylcholanthrene-induced fibrosarcomas, previously demonstrated to contain a common tumor rejection antigen(s), released infectious ecotropic murine leukemia virus and expressed the murine leukemia virus proteins, a glycoprotein with a mol wt of 70,000 (gp70) and an envelope protein with a mol wt of 15,000. To determine whether an antigen(s) specified by a murine leukemia virus might serve as a common tumor rejection antigen(s), primary cultures of syngeneic embryo cells or cultures of an allogeneic embryo cell line were infected with an endogenous ecotropic murine leukemia virus obtained from one of the cross-reacting fibrosarcomas; expression of infectious virus and/or viral proteins by infected and uninfected embryo cells was monitored and correlated with the results of transplantation protection tests. Uninfected allogeneic embryo cells (SC-1) did not release infectious virus or the viral protein gp70; mice immunized with SC-1 cells did not inhibit tumor growth. Uninfected syngeneic embryo cells did not release infectious virus but did release ug quantities of gp70 into supernatant fluids; mice immunized with uninfected syngeneic cells inhibited tumor growth in two of seven experiments. Virus-infected syngeneic and allogeneic embryo cells released both infectious ecotropic murine leukemia virus and gp70; mice immunized with virus-infected cells inhibited tumor growth in 11 of 11 experiments. Growth of the two cross-reacting fibrosarcomas was inhibited in mice immunized with virus-infected embryo cells. The results indicate that antigens coded for by endogenous murine leukemia virus may function as common tumor rejection antigens on chemically induced murine fibrosarcomas. (Author abstract) (35 Refs)

50. MECHANISM OF ACTION OF BCG-TUMOR CELL VACCINES IN THE GENERATION OF SYSTEMIC TUMOR IMMUNITY. I. SYNERGISM BETWEEN BCG AND LINE 10 TUMOR CELLS IN THE INDUCTION OF AN INFLAMMATORY RESPONSE.

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Cancer Metastasis and Treatment Lab., NCI Frederick Cancer Res. Center, Post Office Box B, Frederick, MD, 21701
JNCI; 67(4):853-861 1981

The id injection of a vaccine composed of 10(7) X-irradiated, syngeneic hepatocarcinoma line 10 (L10) cells admixed with 10(8) Mycobacterium bovis strain BCG into inbred Sewall Wright Strain 2 guinea pigs induced a local acute and then chronic inflammatory response. Cellular analysis of enzymatically dispersed dermal vaccination sites and regional lymph nodes revealed quantitative differences between the cellular infiltrate induced by a mixed BCG-tumor cell vaccine and the inflammation induced by either 10(8) BCG alone or 10(7) tumor cells alone. Analysis of dermal sites from Days 1 through 4 following vaccination showed that sites receiving the BCG-tumor cell vaccine contained twofold to fourfold more cells than did those induced by BCG alone and more than fourfold the number of cells induced by L10 cells alone. These results indicated that there was a synergistic interaction between BCG and L10 cells in the induction of an inflammatory response at the site of vaccination. Analysis of the superficial distal axillary lymph nodes draining the site of vaccination revealed a similar synergistic interaction between BCG and L10, such that lymph nodes draining vaccination sites had a greater total cellular content than that induced by either BCG or L10 cells administered separately. When two other tumors, also syngeneic to Strain 2 guinea pigs, were tested for their ability to interact synergistically with BCG to elicit an inflammatory response, it was found that the antigenically distinct hepatocarcinoma Line 1 tumor also shared this characteristic with L10, wheres the L2C B-cell leukemia did not. (Author abstract) (36 Refs)

51. MECHANISM OF ACTION OF BCG-TUMOR CELL VACCINES IN THE GENERATION OF SYSTEMIC TUMOR IMMUNITY. II. INFLUENCE OF THE LOCAL INFLAMMATORY RESPONSE ON IMMUNE REACTIVITY.

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JNCI; 67(4):863-869 1981

The id injection of a vaccine composed of 10(7) X-irradiated syngeneic hepatocarcinoma line 10 (L10) cells admixed with 10(8) Mycobacterium bovis strain BCG into inbred Sewall Wright Strain 2 guinea pigs induces a local inflammatory reaction and effectively immunizes against a contralateral challenge with viable L10 cells. The relationship between the local inflammatory reaction and the generation of tumor immunity was studied. Immunization against L10 was most effective when both L10 cells and BCG were injected into the same site, less effective when they were injected into separate sites with common lymphatic drainage, and not effective when they were injected at totally separate sites. Enzymatic dissociation of dermal vaccination sites revealed that vaccination with BCG and L10 cells combined induced a significantly greater inflammatory response than did vaccination with BCG alone or L10 cells alone; the inflammatory response was also greater than the combination of these individual responses, suggesting that BCG and L10 cells interacted synergistically in the elicitation of an inflammatory response. Sites receiving a combined vaccine of BCG and L10 cells were infiltrated rapidly by inflammatory cells, and surgical excision of these sites as early as 24 hr after vaccine administration did not affect significantly the development of immune responsiveness. However, vaccination sites induced by the injection of BCG and L10 cells at separate but adjacent sites were slowly infiltrated by inflammatory cells, and surgical removal of these sites within 96 hr of vaccination inhibited later immune responsiveness. Quantitative cellular analysis of these inflammatory reactions showed that inflammation was related to tumor-reactive immunity such that the greater the initial inflammatory process, the greater the resistance to tumor challenge. (Author abstract) (36 Refs)

ADOPTIVE IMMUNIZATION AND RELATED APPROACHES

52. LYSIS OF FRESH AND CULTURED AUTOLOGOUS TUMOR BY HUMAN LYMPHOCYTES CULTURED IN T-CELL GROWTH FACTOR.

Lotze MT, Grimm EA, Mazumder A, Strausser JL, Rosenberg SA
Surgery Branch, NCI, NIH, Bethesda, MD, 20205
Cancer Res; 41(11,part1):4420-4425 1981

Human lymphocytes derived from the peripheral blood of patients with a variety of cancers were grown in T-cell growth factor (TCGF) and tested in a 4-hr 51Cr microcytotoxicity assay against fresh and cultured autologous tumor, autologous cultured skin fibroblasts, and autologous fresh peripheral blood lymphocytes. Lymphocytes grown in TCGF caused significant lysis of autologous cultured tumor and fibroblasts but caused little lysis of fresh autologous peripheral blood lymphocytes in all of seven patients tested. This lytic activity against autologous cultured cells was not dependent on the source of serum used in culturing the lymphoid cells or the targets. Lymphoid cells grown in TCGF also were capable of causing selective lysis of fresh autologous tumor cells that had never been in culture in five of nine patients. Lymphoid cells growing in lectin-free TCGF caused selective lysis of autologous tumor in five of seven patients. These observations demonstrate that peripheral lymphoid cells grown in TCGF can be lytic for autologous cultured and autologous fresh tumor compared to the lysis of fresh autologous peripheral blood lymphocytes. The fact that these autoreactive cells, lytic for tumor, may be expanded to large numbers in TCGF suggests a possible role for these cells in studies of the control of the cytotoxic response of activated cells to tumor and possibly in the immunotherapy of tumors as well. (Author abstract) (37 Refs)

53. T CELL-MEDIATED IMMUNOSUPPRESSION AS AN OBSTACLE TO ADOPTIVE IMMUNOTHERAPY OF THE P815 MASTOCYTOMA AND ITS METASTASES.

Dye ES, North RJ
Trudeau Inst., Inc., Saranac Lake, NY, 12983
J Exp Med; 154(4):1033-1042 1981

T-cell immunosuppression in the presence of P815 mastocytoma and effects of passive transfer of sensitized T cells into the tumor host were examined in semisyngeneic male and female B6D2, CB6, DBA/2, and BALB/c mice. Growth of P815 mastocytoma evoked the generation of a state of T cell-mediated immunosuppression; it was possible to regress the P815 mastocytoma by passive transfer of tumor-sensitized T cells only if the tumors were growing in recipient mice that had been made T cell-deficient by thymectomy and gamma irradiation. Regression of the tumor was inhibited by an infusion of splenic cells from T cell-intact tumor-bearing donors. All T cell-deficient mice that received immune spleen cells 4 hr after removal of their day-6 primary tumors survived a 60-day observation period and remained free of palpable tumor metastases, while the recipients of normal spleens all died of tumor metastases with a median survival time of 19 days. Suppressor cells might inhibit the replication of passively transferred immune T cells, and thereby prevent these cells from reaching a number sufficient to cause tumor regression. Delaying the time of infusion of suppressor cells or infusing a smaller number allows enough time for the infused immune cells to expand in number in response to antigens supplied by the recipient's growing tumor. Results are similar to those previously obtained with the chemically induced Meth A fibrosarcoma. (7 Refs)

SEROTHERAPY AND RELATED APPROACHES

54. MONOCLONAL ANTIBODIES TO HUMAN PROSTATE AND BLADDER TUMOR ASSOCIATED ANTIGENS (MEETING ABSTRACT).

Starling JJ, Sieg SM, Wright GL
Eastern Virginia Medical School, P.O. Box 1980, Norfolk, VA, 23501
In Vitro; 17(3):224 1981

Monoclonal antibodies to human prostate adenocarcinoma membrane antigens were produced by fusion of spleen cells from BALB/c mice immunized against the prostate adenocarcinoma cell line, DU145, and the P3-X63-Ag8 (P3) myeloma line or the non-secreting 653 variant of the P3 line. The hybrids were screened for antibody production using a solid-phase in vitro binding radioimmunoassy (RIA). Some hybrids produced antibody specific for the immunizing tumor cells and others produced antibody cross-reactive against several tumors, but not normal cell lines. One of these hybrid lines (DU83.21) secreted antibody that preferentially bound to prostate tumor cells and bladder tumor cells and exhibited weak or no binding to 40 other tumor and normal cell lines tested by RIA. Conventional and competitive binding studies suggest the DU83.21 antibodies do not bind to alpha-fetoprotein, carcinoembryonic antigen, prostatic acid phosphatase, HLA, or DR antigens. Biochemical characterization of the prostate adenocarcinoma membrane antigens is in progress and will be accomplished by immunoprecipitating detergent soluble 125I-labeled cell surface antigens with the DU83.21 monoclonal antibodies followed by sodium dodecyl sulfate gel electrophoresis and autoradiography. (no Refs)

55. DEVELOPMENT OF A MONOCLONAL ANTIBODY AGAINST A TUMOR-ASSOCIATED ANTIGEN (MEETING ABSTRACT).

Peng WW, Bressler JP, Tiffany-Castiglioni E, De Vellis J, Hall W
University of California Los Angeles, Los Angeles, CA, 90024
In Vitro; 17(3):225 1981

A monoclonal antibody-producing hybrid cell line has been obtained by fusing mouse myeloma cells with spleen cells from a mouse previously immunized with C6 rat glioma cells. The antibody was determined to be IgG by immunofluorescence microscopy. Cell surface binding studies with 125I-protein A indicated that this antibody recognizes C6 rat glioma cells, rat B104 neuroblastoma cells, and spontaneously or chemically transformed oligodendrocytes and astrocytes. It also binds to human glial tumor cells. On the other hand, it does not recognize (a) normal rat cell lines of skin fibroblasts or astrocytes, and (b) primary cultures of oligodendrocytes or astrocytes. A weak binding of this antibody occurred on two rodent hepatoma cell lines, H-4-II-E-C3 and Hepa 1, as well as on primary rat hepatocyte cultures. Direct tissue binding experiments indicated that this antibody does not bind to normal rat brain tissue, although some binding to liver cells is observed. We conclude that this antibody binds to a specific cell surface antigen which is absent on normal brain tissues but is present on all the rat and human neural tumor cell lines studied. (no Refs)

56. IMMUNOPOTENTIATION OF TUMOR-BEARING AND TOXOHORMONE-TREATED MICE BY HUMAN CERULOPLASMIN.

Itoh O, Torikai T, Satoh M, Okumura O, Osawa T
Div. Chemical Toxicology and Immunochemistry, Faculty Pharmaceutical Sciences, Univ. Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113, Japan
Gan; 72(5):673-678 1981

Human ceruloplasmin was shown to have a restorative effect on the decrease of delayed hypersensitivity in sarcoma-180-bearing mice and of helper T-cell activity in cell-free Ehrlich cancerous ascitic fluid-treated mice. Furthermore, it was also shown that ceruloplasmin augments the in vivo generation of alloreactive cytotoxic cells which consist of cytotoxic T-lymphocytes, cytotoxic macrophages and K cells. (Author abstract) (36 Refs)

OTHER BIOLOGICAL RESPONSE MODIFIERS

57. IN VIVO IMMUNOSTIMULATING PROPERTIES OF TWO RETINOIDS: RO 10-9359 AND RO 13-6298.

Hercend T, Bruley-Rosset M, Florentin I, Mathe G
Institut de Cancerologie et d'Immunogenetique, Hopital Paul-Brousse, F-94800 Villejuif, France
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

The effects of Ro 10-9359 and Ro 13-6298 on various aspects of immune cell activation and immune system responsiveness to certain challenges were examined in several strains of mice. The incidence and histological type of tumors in both treated and untreated mice were recorded and compared in mice that died or were sacrificed for other testing; Ro 10-9359 appeared to significantly decrease or delay the appearance of tumors. (16 Refs)

58. ADJUVANT EFFECT OF VITAMIN A PALMITATE AND ANALOGS ON CELL-MEDIATED IMMUNITY.

Athanassiades TJ
Dept. Pathology, Downstate Medical Center, State Univ. New York, Post Office Box 25, 450 Clarkson Ave., Brooklyn, NY, 11203
JNCI; 67(5):1153-1156 1981

The sc route was used to study the adjuvant effect of vitamin A palmitate (VA) and the retinoids isotretinoin (Ro 4-3780), etretinate (Ro 10-9359), and motretinide (Ro 11-1430) on cell-mediated immunity to sheep RBC (SRBC) in outbred Mai:NIH(S) mice. The immune response was quantified by a sensitive assay procedure in which the antigen is injected intracutaneously into the pinna of the mouse, and the subsequent inflammatory swelling is measured with calipers. A single simultaneous injection of 150 ug VA enhanced cell-mediated immunity to SRBC as early as 3 days following immunization, and the enhancement persisted for at least 3 wk. Administered as a single injection 1 day or more before or after SRBC or as an ip injection, VA was not effective. Single injections of 100 ug isotretinoin and motretinide but not etretinate also enhanced the response. The effective agents possessed adjuvanticity comparable in magnitude to that of Bordetella pertussis vaccine. (Author abstract) (19 Refs)

CLINICAL IMMUNOLOGY

59. CELL-MEDIATED IMMUNE REACTIONS IN THREE PATIENTS WITH MALIGNANT LYMPHOPROLIFERATIVE DISEASES IN REMISSION AND ABNORMALLY HIGH EPSTEIN-BARR VIRUS ANTIBODY TITERS.

Masucci MG, Szigeti R, Ernberg I, Bjorkholm M, Mellstedt H, Henle G, Henle W, Pearson G, Masucci G, Svedmyr E, Johansson B, Klein G
Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4292-4301 1981

Two patients with Hodgkin's disease in remission and one chronic lymphatic leukemia patient with extraordinarily high anti-Epstein-Barr virus (EBV) (viral capsid antigen) antibody titers (greater than 10,000) were selected to study a spectrum of cell-mediated immune responses, including natural killer, interferon-boosted killer, antibody-dependent lymphocytotoxicity, and T-cell-mediated reactions. The purpose was to compare these reactions in patients with immunosuppression and a high EBV load who can hold their EBV-carrying cells under control with the corresponding reactions in patients with EBV-carrying lymphoproliferative disease. In contrast to the latter group, the three patients of the present study showed a less profound and less general suppression of the immune responses. Multiple effector mechanisms probably safeguard against the proliferation of EBV-transformed B-cells. Clinically manifest EBV-carrying lymphoproliferative disease occurs only in very severe immunodeficiencies effecting multiple effectors. (Author abstract) (44 Refs)

60. DOCUMENTATION OF EPSTEIN-BARR VIRUS INFECTION IN IMMUNODEFICIENT PATIENTS WITH LIFE-THREATENING LYMPHOPROLIFERATIVE DISEASES BY EPSTEIN-BARR VIRUS COMPLEMENTARY RNA/DNA AND VIRAL DNA/DNA HYBRIDIZATION.

Saemundsen AK, Purtilo DT, Sakamoto K, Sulllivan JL, Synnerholm AC, Hanto D, Sim mons R, Anvret M, Collins R, Klein G
Dept. Tumor Biology, Karolinska Inst., 104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4237-4242 1981

Tissues from patients thought to have Epstein-Barr virus (EBV)-induced lymphoproliferative diseases were probed for EBV genomes using two independent hybridization techniques. Tissues from six patients with the X-linked lymphoproliferative syndrome, all five renal allograft recipients with immunoblastic sarcoma, and eight patients with diverse types of immunodeficiency and lymphoproliferative diseases such as fatal infectious mononucleosis or malignant lymphoma associated with antecedent immunodeficiency contained significant numbers of EBV genome equivalents per cell. The use of two hybridization probes is recommended to confirm the presence of EBV genomes. The finding of significant numbers of EBV genomes in tissues from patients with immunodeficiency suggests that EBV is the etiological agent of the associated lymphoproliferative diseases. (Author abstract) (53 Refs)

61. DOCUMENTATION OF EPSTEIN-BARR VIRUS INFECTION IN IMMUNODEFICIENT PATIENTS WITH LIFE-THREATENING LYMPHOPROLIFERATIVE DISEASES BY CLINICAL, VIROLOGICAL, AND IMMUNOPATHOLOGICAL STUDIES.

Purtilo DT, Sakamoto K, Saemundsen AK, Sullivan JL, Synnerholm AC, Anvret M, Pritchard J, Sloper C, Sieff C, Pincott J, Pachman L, Rich K, Cruzi F, Cornet JA, Collins R, Barnes N, Knight J, Sandstedt B, Klein G
Dept. Pathology Lab. Medicine, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Cancer Res; 41(11,part1):4226-4236 1981

Multiple methods, pedigree analysis, clinical evaluation, and Epstein-Barr virus (EBV)-specific serology, EBV DNA hybridization of tissues to probe for viral genome, staining of touch imprints for EBV nuclear-associated antigen, establishment of spontaneous infected B-cell lines from peripheral blood or tissues, examination of peripheral blood smears, and hematopathology studies, were used to study seven patients with the X-linked lymphoproliferative syndrome and seven additional patients with life-threatening EBV-associated diseases. These studies demonstrated EBV in the tissues of all 14 patients and immunodeficient antibody responses to EBV were documented. This virus can produce various life-threatening lymphoproliferative diseases in a variety of immunodeficient patients. (Author abstract) (35 Refs)

62. CELLULAR IMMUNE DEFECTS TO EPSTEIN-BARR VIRUS-DETERMINED ANTIGENS IN YOUNG MALES.

Masucci MG, Szigeti R, Ernberg I, Masucci G, Klein G, Chessels J, Sieff C, Lie S, Glomstein A, Businco L, Henle W, Henle G, Pearson G, Sakamoto K, Purtilo DT
Dept. Tumor Biology, Karolinska Inst., S 104 01 Stockholm 60, Sweden
Cancer Res; 41(11,part1):4284-4291 1981

Three males with the X-linked lymphoproliferative syndrome (XLP) with hypo- or a gammaglobulinemia following Epstein-Barr virus (EBV) infection and two males with the chronic mononucleosis syndrome were investigated for immune responses to EBV-determined antigens. Males with XLP showed profound cellular immune defects. Markedly diminished responses of natural killer cell and interferon-activated killer cell activities and impaired WBC migration inhibition responses to phytohemagglutinin were determined in patients with XLP. The two patients with chronic mononucleosis showed less severe defects. All patients showed partial or complete impairment of their EBV-specific immune responses as measured by WBC migration inhibition. EBV-specific antibodies were markedly diminished against EBV-associated nuclear antigen, early antigen, and viral capsid antigen in males with XLP. In contrast, patients with chronic mononucleosis had elevated antibodies to most EBV-specific antigens. Individuals with life-threatening EBV-induced lymphoproliferative disorders may exhibit multiple defective immune mechanisms against the virus. (Author abstract) (44 Refs)

63. HUMAN NATURAL KILLER CELL ACTIVITY IN PATIENTS WITH ACUTE LEUKEMIA AND APLASTIC ANEMIA UNDERGOING BONE MARROW TRANSPLANTATION (MEETING ABSTRACT).

Lau WK, Ching CY
University of Hawaii School of Medicine, Honolulu, HI
Program and Abstracts of the 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, November 4-6, 1981, Chicago, Illinois American Society for Microbiology; :A254 1981

We studied natural killer (NK) cell activity in 9 prospective allogeneic bone marrow transplant (BMT) candidates (6 patients with acute leukemia, 3 patients with aplastic anemia). NK cell activity was studied using herpes virus infected fibroblast (NK (HSV-D)), uninfected fibroblast (NK (FS)), and chronic myelogenous leukemia (NK (K562)) targets. Enhancement of NK cell function using interferon was attempted. Pretransplant NK (HSV) activity was low in 8 of 9 patients tested; interferon induction increased NK (HSV) function in 2 assays. Pretransplant NK (FS) activity was low in all patients assayed (only one assay increased with interferon induction). NK (K562) activity was low in 3 of 4 patients tested (one assay increased with interferon induction). Five of our patients underwent allogeneic BMT from HLA identical, MLC compatible sibling donors. NK (HSV-1), NK (FS), and NK (K562) function spontaneously returned to normal levels post transplantation except in one patient. All patients who developed graft versus host disease had low pre-transplant NK activity except for one patient who was in complete remission. NK activity was normal during viral infections (ie, dessiminated herpes zoster, cytomegaloviral pneumonitis and adenoviral hemorrhagic cystitis). (no Refs)

64. NEW ANTIGENIC DETERMINANT COMMON TO HUMAN THYMUS LEUKAEMIA-ASSOCIATED ANTIGENS AND COMMON ACUTE LYMPHOBLASTIC LEUKAEMIA ANTIGEN.

Negoro S, Yoshizaki K, Henderson ES, Seon BK
(c/o Seon) Dept. Immunology Res., Roswell Park Memorial Inst., Buffalo, NY, 14263
Clin Exp Immunol; 45(3):487-495 1981

In the present paper we demonstrate that there is an antigenic determinant common to two different types of human leukemia-associated antigens, ie human thymus leukemia-associated (HTL) antigens and common acute lymphoblastic leukemia (cALL) antigen. In addition, there are distinct antigenic determinants which are unique to the HTL antigens or to the cALL antigen. The new, common antigenic determinant will be useful as a new differentiation marker of human hematopoietic cells as well as a new leukemia-associated marker. In the present study, we used several different anti-human leukemia antisera which include those prepared by immunizing rabbits (Numbers 7549 and 7550) with purified HTL antigens. The antisera 7549 and 7550, without any absorption, showed strong specificity as well as strong antibody activity toward leukemia cells. These are the first anti-human leukemia antisera, except for the monoclonal hybridoma antibodies, that show good specificity for leukemia cells without prior absorption. (Author abstract) (33 Refs)

65. DEFINITION OF THE HIGH-RISK ACUTE LYMPHOBLASTIC LEUKEMIA PATIENT BY IMMUNOLOGICAL PHENOTYPING WITH MONOCLONAL ANTIBODIES.

Zipf TF, Fox RI, Dilley J, Levy R
(c/o Levy) Dept. Medicine/Oncology, Stanford Univ., Stanford, CA, 94305
Cancer Res; 41(11,part2):4786-4789 1981

An accurate method of classification of the surface membrane characteristics of blast cells from patients with acute lymphoblastic leukemia would allow a more definitive study of the nature of this disease. Monoclonal antibodies have been produced to the surface antigens of leukemic blasts from a patient with high-risk acute lymphoblastic leukemia. Two antibodies of interest were obtained from this immunization. These two, in combination with a monoclonal antibody with anti-Ia specificity, have been used to obtain surface phenotypes for patients with childhood acute lymphoblastic leukemia. Preliminary results indicate that the definition of a high-risk group, using these antibodies, is possible. (Author abstract) (16 Refs)

66. EFFECTS OF CANCER TREATMENT ON IMMUNE COMPETENCE AS QUANTITATED BY IN-VIVO AND IN-VITRO TESTS OF CELL MEDIATED IMMUNITY (MEETING ABSTRACT).

Ghossein NA, Kadish AS, Bosworth JL
Department of Radiology, Division of Radiotherapy, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Ave., Bronx, NY
Long Term Normal Tissue Effects of Cancer Treatment, April 13-15, 1981, Bethesda, Maryland Committee for Radiation Oncology Studies; 1981

The occurrence of delayed sensitivity reaction denotes a state of T cell immunity. Skin reactivity to 2-4 Dinitrochlorobenzene (DNCB) is an indication that the patient is able to develop a cell mediated immunity to this hapten, to which most people have not been exposed previously. In order to determine if radiotherapy alters the skin reactivity to DNCB, we have evaluated 686 patients prior to radical radiotherapy for a localized cancer. Three to 6 mo following completion of irradiation, there was significant increase in the incidence of the positive reactors when they were challenged with another 50 ug. Only 9% became negative following radiotherapy, whereas 40% of the initially non-reactors became positive. It appears that localized radical radiotherapy does not deleteriously alter the cell mediated immunity of cancer patients, as determined by skin reactivity to DNCB. In order to determine the effect of irradiation on the inflammatory component of the immune response, 197 patients with localized cancer were skin tested with Croton oil. Over 60% of those who had a negative response became reactive afterward. Natural cytotoxicity against K562 target cells was measured in 75 patients with solid epithelial malignant tumors. Of 50 patients studied prior to radiotherapy, 16 (32%) failed to kill normally. Of 41 patients tested 4 to 6 wk following completion of radiotherapy, 11 (27%) failed to kill. Most of the non-killers fell into the advanced disease category, regardless of whether or not they had received irradiation. Of patients with localized tumors, 12% of non-irradiated and 13% of radiated patients failed to exhibit normal natural killer (NK) activity. Of patients with advanced cancers, 48% of non-irradiated patients and 44% of irradiated patients failed to kill. Peripheral blood lymphocytes from both radiated and non-radiated patients showed enhanced cytotoxicity after pretreatment with interferon. These results indicated that radiation therapy had no significant effect on natural cytotoxicity. (no Refs)

67. SERUM-ASSOCIATED INHIBITION OF NEUTROPHIL FC RECEPTORS IN CANCER PATIENTS.

Patrone F, Dallegri F, Gremmo A, Bonvini E, Migliorini P, Cantarella S, Ferrarini M, Sacchetti C
Dept. Medicine, Univ. Genoa Medical Sch., Viale Benedeto XV, n. 6, Genoa 16132, Italy
JNCI; 67(4):803-807 1981

Rosettes with ox RBC coated with purified IgG antibody were used to detect Fc receptors on neutrophils from 60 patients with solid neoplasias and from 55 normal controls. The mean av of the rosettes in the patients was 48.10%, and that in normal controls was 79.42%, with a highly significant difference according to the Wilcoxon test [negative probability, p(w) = 4.47 x 10(-5)]. The low proportion of patients' rosettes was related to the presence of a serum factor, which also inhibited normal neutrophil rosette formation. Patient neutrophils (or normal neutrophils treated with patient sera) recovered their rosetting capacity when cultured in vitro. No correlation was found between low percentages of rosette-forming cells and the level of circulating immune complexes of the individual patients. Additional evidence also supported the finding that IC and the serum factor are probably unrelated. (Author abstract) (31 Refs)

68. MEASUREMENTS OF CIRCULATING IMMUNE COMPLEXES IN CANCER PATIENTS (MEETING ABSTRACT).

Wilson RE, Rayner AA, Rodrick ML, Harte PJ, Munroe AE, Steele GD
Department of Surgery, Harvard Medical School, Boston, MA
Eur Surg Res; 13(1):32 1981

We have modified the technique for aggregation of circulating immune complexes (CIC) by polyethylene glycol (PEG 6000) which permits reproducible measurements by an increase in optical density (OD 450 nm) and is not dependent on the class of immunoglobulin or the ability of the complexes to bind complement. We have compared the levels of CIC in normal human serum with those in the serum of patients with cancer and rheumatoid arthritis. In the cancer population, measurements have been made before and after surgical procedures -in patients with resectable or unresectable lesions-and in patients with or without sepsis. Patients with cancer had significantly higher PEG-CIC values than normals and lower values than rheumatoids. Patients with infection had significantly higher levels than normal while cancer patients with infection had significantly higher PEG-CIC levels than those with either cancer or infection alone. While mean preoperative values for patients with resectable and unresectable cancer were not different, PEG-CIC levels fell significantly in patients whose cancers were successfully resected. Patients with incompletely resected malignancy showed no change in CIC levels in the postoperative sera. It is hoped that serial measurement of PEG-CIC in individual patients may provide more useful data and permit correlation of CIC levels with changes in tumor vol. The possibility exists that levels of CIC in the serum can provide a record of biological events in cancer patients including tumor growth, response to treatment and cancer recurrence. (no Refs)

69. INTERPRETATION AND IN VIVO RELEVANCE OF LYMPHOCYTOTOXICITY ASSAYS.

Klein E
Tumor Biology Dept., Karolinska Institutet, 104 Stockhom 60, Sweden
Haematol Blood Transfus; 26:345-350 1981

This review deals with human and and murine natural killer (NK) cells, interferon activation of NK cells, generation of NK cells in culture, detection of cytotoxic T cells in the blood of acute infectious mononucleosis patients, in vitro NK cell activity against autologous tumors, and the therapeutic implications of immunologic recognition of such tumors. (32 Refs)

70. EFFECTS OF ANESTHESIA AND OPERATIONS ON IMMUNE COMPETENCE (MEETING ABSTRACT).

Chretien PB
Department of Surgery, University of Maryland School of Medicine, Baltimore, MD, 21201
Long Term Normal Tissue Effects of Cancer Treatment, April 13-15, 1981, Bethesda, Maryland Committee for Radiation Oncology Studies; 1981

Patients who were sensitized to dinitrochlorobenzene preoperatively but had surgical therapy of their malignancy prior to the interval required for manifestation of an immune response to challenge with this immunogen frequently failed to respond to the challenge. Observations prompt the hypothesis that a similar inhibition of antitumor specific mechanisms are incurred during this same interval in patients undergoing surgical therapy of cancer. In mice bearing primary tumors, and increased incidence of distant metastases that followed anesthesia and surgical manipulation did not occur in animals that received the immune reconstituting agent, thiabendazole. In a controlled clinical evaluation of levamisole, among patients who had resection of advanced lung cancers, the incidence of postoperative distant metastases was lower in those who received the agent during and after operation. Similar results were obtained with the interferon inducer poly A - poly U in patients who had resection of breast cancer. An important finding in these experiments was that the incidence of local tumor recurrences was not diminished in patients receiving these drugs. Relevant here is evidence that this also is the primary deleterious effect on the host-tumor relationship of radiation therapy and chemotherapy in the treatment of solid malignancies. Results of current research which indicate that this facilitation to the development of distant metastases can be ameliorated by immune reactive agents which modulate rather than stimulate immune mechanisms provide rationale for evaluation of these agents as adjuvants to therapies which have as their principal effect the eradication of the primary malignancy. (no Refs)

REVIEWS

71. MODULATION OF THE IMMUNE RESPONSE BY CHEMOTHERAPY.

Braun DP, Harris JE
Section Medical Oncology, Dept. Medicine, Dept. Immunology, Rush-Presbyterian-St. Luke's Medical Center, 1753 W. Congress Parkway, Chicago, IL, 60612
Pharmacol Ther; 14(1):89-122 1981

The effects of drugs on immune response are reviewed. Immune response may be impaired or augmented by various drug treatments. Factors relevant to drug-induced immunosuppression include pharmacological action and pharmacokinetics of the drug, dosage and schedule of administration, the nature of the immune response investigated, and the influence of antigen administration schedule. Drugs may affect afferent immune responses, including the numbers and immunocompetence of monocytes, macrophages, and lymphocytes. Drugs may affect the central, or productive phase of immune response, including DNA synthe sis and the differentiation of suppressor and effector cells. Effects on the efferent portion of immune response include changes in mature T cells and non-T cell-non-B cell effector functions. The effects of drugs may be affected by the condition of immune response prior to drug administration. Consideration of all these effects should facilitate design of therapies. (268 Refs)

72. IMMUNOBIOLOGY AND IMMUNOTHERAPY OF COLORECTAL CANCER.

Papermaster BW
Cancer Res. Center, Columbia, MO
Cancer Bull; 33(4):135-140 1981

Immunocompetence evaluation in colorectal cancer patients, immunotherapy protocols (strategy and results), and animal models and laboratory studies are presented. Although immunocompetence data are difficult to compare because of variation in study techniques, information increasingly indicates association of progressive immunodeficiency with advancing stage of disease. Some degree of immunodeficiency is already definable in a certain group of patients by the time they have Dukes' B disease. More consistent manifestation of immunodeficiency, particularly in the T-cell category, occurs as tumor progresses. The developmen of monoclonal antibodies and cytofluorometry should allow more precise categorization of T-cell defects. Increased peripheral blood immune responsiveness to ongoing colon cancer has been shown by leukocyte adherence inhibition (LAI). LAI has been correlated with tumor progression, development, and resection. Test results reflect alterations in the lymphoid system detectable by LAI and are correlated with progressive colon cancer. Results of immunotherapy trials suggest that advances in colon cancer therapy will occur at the adjuvant level, with immunotherapy acting as a supplement to established chemotherapeutic modalities rather than replacing them. Two animal model systems, the MCA38 mouse transplantable tumor and dimethylhydrazine treatment of rats, appear promising for the study of colon neoplasms. Analysis of lymphocyte populations and the use of monoclonal antibodies to colon carcinoma antigens are discussed. (34 Refs)

73. MONOCLONAL ANTIBODIES: THE NEXT ATTEMPT AT TUMOR IMMUNOTHERAPY.

Boman BM, Fathman CG
Mayo Graduate Sch. Medicine, Rochester, MN
Mayo Clin Proc; 56(10):641-644 1981

Production of monoclonal antibodies (MAs) and their potential applications in cancer immunotherapy are discussed. The MAs are obtained by the fusion of mouse myeloma cells with splenocytes from mice immunized with tumor cells. Cells secreting the desired tumor antibody can be cloned by limiting dilution and maintained in culture indefinitely. Once MAs specific for tumor antigens have been identified, recombinant genetic engineering might be used to obtain bacteria that produce the antibody variable region containing the tumor antigen binding site. Conjugates of chemotherapeutic agents, radioisotopes , or plant toxins and MAs may provide the specificity needed for effective in vivo antitumor activity. Pharmacokinetic factors that influence the efficacy of antibody therapy are summarized. (21 Refs)

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CLINICAL CANCER IMMUNOLOGY AND IMMUNOTHERAPY

SERIES CT06 No. 82/04

APRIL, 1982

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CLINICAL TRIALS

1. LEVAMISOLE AS AN IMMUNOSTIMULANT IN PATIENTS WITH PRIMARY LUNG CANCER.

Krzysko R, Slowik-Gabryelska A
Wojewodzki Zespol Specialistyczny Chorob Pluc i Gruzlicy, ul. Mielzynskiego 31b, 61-725 Poznan, Poland
Pneumonol Pol; 49(1):29-34 1981

Thirty-six anergic patients with inoperable primary lung cancer were treated with levamisole (150 mg/day on 3 consecutive days). Anaplastic carcinoma was diagnosed in 23 cases, squamous epithelial carcinoma in 10, and adenocarcinoma in 3. A control of 31 patients with inoperable lung cancer (20 with anaplastic carcinoma, 11 with squamous epithelial carcinoma) and received telecobalt and chemotherapy. The tuberculin test was negative at the beginning in all 36 patients. Failure of the test to turn positive after 5 levamisole cycles disqualified the patients from further immunotherapy with BCG. Even patients survived less than 7 mo, and 7 survived more than 12 mo. In the control group, 29/31 patients survived less than 7 mo, and 1/31 survived 12 mo. The tuberculin test remained negative after the levamisole treatment in 7/36 patients; the frequency of conversion was 100% in Stage I, 94% in Stage II, and 50% in Stage III. Immunostimulation with levamisole made the subsequent immunotherapy more effective and safer. It also helped select cases in which immunotherapy can be dangerous (patients who did not respond to the levamisole treatment). (16 Refs) (In POL)

2. RANDOMIZED CONTROL STUDY OF LEVAMISOLE IN TREATMENT OF LUNG CANCER (MEETING ABSTRACT).

Ota K, Nishimura M, Morishita M, Urata A
Aichi Cancer Center, Nagoya, Japan
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

The effect of immunotherapy with levamisole in the treatment of 69 cases with inoperable advanced lung cancer was studied by randomized control trial. Levamisole was given at a daily dose of 150mg per body for consecutive 3 days every 2 wk. In 28 cases with squamous cell carcinoma (sq c ca) combination chemotherapy of METT, consisting of mitomycin C (MMC) 0.04mg/kg, cyclophosphamide (CPA) 2mg/kg, thio-TEPA 0.2mg/kg and chromomycin A3 (CHM) 0.01mg/kg, was given every 4 days simultaneously with radiotherapy of 5,000 rads in total, in 10 cases with adenocarcinoma (adenoc), MFC, consisting of MMC 0.08mg/kg, 5-Fluorouracil (5-FU) 10mg/kg and cytosine arabinoside (ara-C) 0.8mg/kg, was given weekly simultaneously with radiotherapy of the same rads in total, and in 31 cases with large and small cell carcinoma, METVFC, consisting of MMC 0.04mg/kg, CPA 2mg/kg, CHM 0.01 mg/kg, vincristine 0.02mg/kg, 5-FU 10mg/kg and ara-C 0.8mg/kg, was given weekly simultaneously with radiotherapy of the same rads in total. The survival rate of the levamisole group in sq c ca was significantly superior to the control group, and that of the levamisole group in adenoc was slightly superior to the control group, but no significant difference was observed in the survival rate in large cell and small cell carcinoma. The side effect of levamisole such as agranulocytosis was not observed. Judging from the present randomized control study, in summary, the immunotherapy with levamisole combined with chemoradiotherapy for inoperable advanced lung cancer can be said to enhance the survival rate in sq c ca and adenoc of the lung. (no Refs)

3. COMBINATION CHEMOTHERAPY, RADIOTHERAPY AND BCG IMMUNOTHERAPY IN LIMITED SMALL CELL CARCINOMA OF THE LUNG (MEETING ABSTRACT).

McCracken JD, Chen T, White J
Southwest Oncology Group Study, 3500 Rainbow Blvd., Suite 100, Kansas City, KA, 66103
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

From November 1976 to March 1979 the Southwest Oncology Group treated 298 patients with limited (disease confined to the chest and encompassed by one radiotherapy port) small cell carcinoma of the lung with combination chemotherapy and radiotherapy plus or minus BCG immunotherapy. Two induction chemotherapy programs were utilized: a) cyclophosphamide, vincristine, methotrexate, and fluorouracil; or b) cyclophosphamide, doxorubicin and vincristine. Patients received 4500 rads of radiation therapy to the bulk primary tumor and 3000 rads to whole brain followed by maintenance chemotherapy. Half of all patients were randomized to receive one vial (5 x 10(8)) of high viability Pasteur BCG by scarification technique given on days 8 and 15 of each 21-28 day treatment cycle. Increased granulocytopenia accompanied the addition of BCG immunotherapy. Patients receiving BCG achieved a response of 49% vs those patients not receiving BCG for 44%. Median response duration was 40 wk for the BCG arms and 38 wk for the no BCG arms, and survival was no different, 42 wk for the BCG arms vs 50 wk for the no BCG arms. In patients responding to therapy and surviving greater than one yr, patients continuing to receive BCG therapy demonstrated a slight yet significant survival benefit over those patients not receiving BCG, 93 wk vs 81 wk. It appears that BCG immunotherapy has no beneficial effect on response rate, duration of response, or survival in programs using chemotherapy and radiotherapy for control of limited small cell carcinoma of the lung except in this small group of long term survivors. (no Refs)

4. VINDESINE (V), ADRIAMYCIN (A) AND PLATINUM (P) CHEMOTHERAPY IN EXTENSIVE ADENO AND SQUAMOUS CELL LUNG CANCERS (E-ASCL) (MEETING ABSTRACT).

Valdivieso M, Bedikian AY, Patt YZ, Murphy WK, Umsawasdi T, Carr DT, Hersh EM, Bodey GP, Freireich EJ
University of Texas M. D. Anderson Hospital, Houston, TX
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

One-hundred and two patients (pts) with E-ASCL received either VAP alone (54 pts) or combined to Thymosin Fraction V (T) immunotherapy (VAP-T, 48 pts). Pts characteristics included: median age 56 yr (range, 35-80 yr); males, 73 pts; performance status Zubrod's 0-1, 48 pts; 2, 46 pts; 3-4, 8 pts; prior radiation therapy, 26 pts; greater than 5% pretreatment wt loss, 49 pts; and brain metastases, 18 pts. Pts diagnoses were: adenocarcinoma, 65 pts; squamous carcinoma, 28 pts; and other, 9 pts. Both treatment groups were comparable for major prognostic factors. Drug dosages were: V equals 3 mg/m(2)/d1; A equals 50 mg/m(2)/d1; P equals 60 mg/m(2)/d1; T equals 60 mg/m(2)/d1;4,8,12 and 16. Courses were repeated at 3 wk intervals. Of 99 evaluable pts, there were 33 complete remission (CR) + partial remission (PR) (33%), with a significant response advantage for VAP alone treated pts (45% vs 20%), particularly if they had adenocarcinoma (50% of 36 pts vs 19% of 27 pts). Fourteen additional pts had responses less than PR, 33 pts remained stable and 19 progressed. There were no survival differences between both treatment arms by major prognostic factors. The medium survival duration for responding pts (10 mo) was significantly longer than that of pts who remained stable (8 mo), or progressed (2.5 mo). Toxicities were acceptable and similar for both treatment groups. VAP is an effective treatment for pts with E-ASCL, particularly those with adenocarcinoma. The addition of T did not improve the results of VAP. (no Refs)

5. FAILURE OF SPECIFIC ACTIVE IMMUNOTHERAPY IN LUNG CANCER.

Souter RG, Gill PG, Gunning AJ, Morris PJ

Nuffield Dept. Surgery, John Radcliffe Hosp., Headington, Oxford, England

Br J Cancer; 44(4):496-501 1981

A randomized trial comparing routine follow-up with a treatment regimen aimed at increasing specific anti-tumor immunity has been carried out in 95 patients after total surgical excision of lung cancer (not small-cell). Treatment consisted of inoculation with an autologous irradiated suspension of tumor cells combined with a small dose of C parvum given id during convalescence. Although treatment was associated with virtually no side effects, there has been no apparent benefit and input to the trial has now stopped. (Author abstract) (21 Refs)

6. BCG PLUS LEVAMISOLE FOLLOWING IRRADIATION OF ADVANCED SQUAMOUS BRONCHIAL CARCINOMA (MEETING ABSTRACT).

Pines A

Hertford County and Herts and Essex Hospitals, Hertfordshire, England

Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Patients with squamous carcinoma of the bronchus with locally advanced and inoperable lesions, but without obvious metastases, were irradiated with a dose of at least 4000 rads in an attempt to bring about a cure. An originial series of 48 patients was randomized between controls and patients given BCG at two-weekly intervals. Survival was significantly better for the BCG-treated patients during the first yr only. Three are still alive and well eight to ten yr later. All control patients had died by the end of the third yr. Metastases were common among control patients but not among the BCG-treated group. To improve these results levamisole was given in addition in a dose of 2.5 mg/kg body wt on two days of the wk. Treatment was allocated at random to three groups: control, BCG two-weekly and BCG four-weekly. At the end of the first yr 44% of 27 controls, 50% of 16 patients given levamisole and BCG four-weekly and only 4% of 23 patients given levamisole and BCG two-weekly had died. At the end of the second yr deaths were 66% among the control group and 22% in the levamisole and two-weekly BCG group. In the third and fourth yr deaths were 85% and 74% respectively. The four-weekly BCG regimen had been discontinued. Skin testing with tuberculin and Candida showed some correlation with these results. There were many fewer metastases in the group given BCG two-weekly. BCG two weekly plus levamisole thus appears to give some prolongation of life, though after two yr there is no further benefit. (no Refs)

7. CHEMOIMMUNOTHERAPY FOR MELANOMA WITH DTIC, ACNU, VCR AND OK432: EVALUATION OF NEW COMBINATIONS FOR SURVIVAL RATES, SIDE EFFECTS AND CELLULAR IMMUNITY.

Jimbow K, Yanbe H, Nishio C

Dept. Dermatology, Sapporo Medical Coll., Minami 1, Nishi 16, Sapporo 060, Japan

J Dermatol (Tokyo); 8(4):259-266 1981

The effects of combined chemotherapy [5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, vincristine, and 1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride] and immunotherapy (nonspecific Group A streptococcal preparation OK432) on eight disseminated melanoma patients were evaluated. The patients had primary lesions of histologically verified lentigo-maligna, Stage III or IV; 7/8 patients had lesions belonging to acral and mucosal malignant melanoma and 1/8 had primary occurrence on the back. Controls consisted of 11 Stage III melanoma patients with lentigo-maligna treated by other regimens of chemoimmunotherapy, immunotherapy, radiation, or a combination of these. Survival rates were significantly different at 5 and 8 mo after initiation of treatment from those exhibited by controls; survival period ranged between 5 and 18 mo, including five patients who were still alive. Controls survived 3-15 mo, but all died. Blood picture and liver function tests before and after the trials revealed a decrease in RBC count and increase in serum glutamic oxalacetic transaminase, but the changes were within normal limits. Cellular immunity with specific mitogens of autologous and allogeneic melanoma cells and non-specific mitogens was preserved. Lymphocytes from melanoma patients possessed a high killer cell effect against melanoma cells; the effect was nonspecific as evidenced by the killing of control cells from acute myelocytic leukemia patients. Immunoadjuvant therapy with OK432 appears to affect the cellular immune response in a way similar to BCG. (26 Refs)

8. AUTOIMMUNIZATION IN PATIENTS WITH MALIGNANT MELANOMA (MEETING ABSTRACT).

Sutherland CM, Krementz ET

Tulane University School of Medicine, New Orleans, LA

W.H.O. Seminar on Malignant Melanoma, June 24, 1981, Gothenburg, Sweden. World Health Organization 35 pp., 1981.

Specific active immunotherapy has been studied in patients with malignant melanoma. Fourteen patients with Stage II or Stage III melanoma who could have all of their gross diseases resected and on whom a tissue culture cell line could be established were treated. Autologous tumor cells were harvested, irradiated, mixed with BCG, and administered at two-wk intervals. Between 8 x 10(6) to 58.9 x 10(6) cells were given. Immune response was measured by fluorescent antibody production and by in vitro cytotoxicity. The median disease-free interval was 9.5 mo, the median survival was 23 mo; there was 36% four-yr survival and 29% five-yr survival. The longest survival occurred in patients who developed high titers of antibody. Of those patients who subsequently relapsed, there was a 27% complete remission rate when subsequently treated with chemotherapy. Again, response to chemotherapy correlated well to antibody production. It appears that specific active immunotherapy with tissue cultured autologous tumor cells is a promising method of treatment for malignant melanoma. (no Refs)

9. IMMUNOPHARMACOLOGICAL AND CLINICAL INVESTIGATIONS WITH AN IMMUNOMODULATOR - OK-432-IN PATIENTS WITH MALIGNANT MELANOMA (MEETING ABSTRACT).

Micksche M, Kokoschka EM, Knobler A, Uchida A

Institute fur Cancer Research, Vienna University, Vienna, Austria

W.H.O. Seminar on Malignant Melanoma, June 24, 1981, Gothenburg. Sweden. World Health Organization 35 pp., 1981.

OK-432, a streptococcal preparation developed in Japan has been recently demonstrated to be a potent immune response modifier. We investigated the therapeutic and immunomodulating properties of this preparation in patients with malignant melanoma. Altogether, 35 patients (12 single doses, on application by one route, 15 frequent applications by one route, 7 combined routes) received OK-432 id, im, intrapleurally, ip, iv, respectively. Therapy was well tolerated (side effects noted were fever and chills in patients, especially after iv and intracavitary applications). Clinical outcome of 22 evaluable patients can be considered favorable, in 14 of them. Immunopharmacological studies revealed that iv, id and im route of OK-432 is able to enhance significantly natural killer (NK)-cell activity (4 hr Cr release assay, K 562 target) in treated melanoma patients. Furhter studies showed that it is possible to activate NK-cell activity in vitro by preincubation of patients' lymphocytes with OK-432, cytotoxicity was comparable with that after addition of interferon. Both in vivo and in vitro studies clearly demonstrate that OK-432 is a potent immunomodulator, and, furthermore, there is some evidence for a therapeutic benefit for melanoma patients treated with OK-432 for a longer period of time. (no Refs)

10. IMMUNOTHERAPY OF MALIGNANT MELANOMA AND CHANGES OF IMMUNE PROFILE OF THE PATIENTS (MEETING ABSTRACT).

Kovarik J, Mechl Z, Ninger E, Zemanova D, Lauerova L, Sopkova B

Research Institute of Clinical and Experimental Oncology, Brno, Czechoslovakia

Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

The non-specific adjuvant immunotherapy with BCG vaccine has been assessed in 81 stage I and 51 stage II melanoma patients for 3 and 5 yr respectively. Melanoma patients of various clinical stages were longitudinally followed for immune competence using in vivo cutaneous reactions of delayed hypersensitivity together with a set of in vitro immune tests. The following conclusions were made: the group of stage I melanoma patients receiving postoperatively BCG immunotherapy did not show any significant differences in the percentage of recurrences, disease-free interval, mortality rate and survival time in comparison with the post-surgically untreated group. No therapeutical benefit of adjuvant BCG immunotherapy could be proved in stage II melanoma patients as regards the progression of tumor or the percentage of survivors in comparison to the control groups treated with either surgery alone or postsurgical chemotherapy. Prognostic value of the non-specific immune tests appeared to be rather small in patients in the initial stages of melanoma. The frequency of depressed immune parameters increased mostly at the advanced stages of the disease. It suggested that the immune deficiency in melanoma patients was usually a consequence of the progression. (no Refs)

11. REDUCED INCIDENCE OF LOCO-REGIONAL RECURRENCES IN MELANOMA USING BCG IMMUNOTHERAPY AFTER SURGERY (MEETING ABSTRACT).

Paterson AH, Williams D, Jerry LM, McPherson TA

Cross Cancer Institute, Alberta T5G 1Z2, Canada

Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

A prospectively controlled, randomized clincal trial was carried out to determine whether a combination of local perilesional id and systemic oral BCG immunotherapy given after surgery to patients with early melanoma would reduce the overall recurrence rate and improve survival. Patients with Stage I melanoma, Clark's Level (CL) 3-5 were eligible for trial entry, and after surgical wide excision and consent, were randomly allocated to either routine follow-up or adjuvant BCG immunotherapy. Immunotherapy consisted of id BCG 40 mg by Heaf Gun around the site of local surgery followed by oral BCG 40 mg for 5 days each mo for one yr. ID BCG was then repeated at the same site and oral BCG was continued for one further yr. One hundred and fifty-eight patients were entered into the trial: 79 in the treatment group (of whom 53 were CL 3, 23 were CL 4, and 3 were CL 5) and 79 in the control group (of whom 51 were CL 3, 25 were CL 4 and 3 were CL 5). There have been 36 recurrences: 14 in the treatment group and 22 in the control group. Twenty-one patients have died: 9 in the treatment group and 13 in the control group. Using this form of immunotherapy, there has been a significant reduction in the incidence of local and regional recurrences as site of first recurrence (5 BCG vs 17 control) but not of distant metastases (9 BCG vs 5 control). The overall recurrence rates show a trend in favor of the BCG group, which is entirely due to the reduction of loco-regional recurrences in this group. (no Refs)

12. IMMUNOTHERAPY OF ACUTE LEUKEMIA PATIENTS.

Riabov NV, Riabova TI, Voronchikhina LD, Klestova VI, Bykova LI

Res. Inst. Blood Transfusion, Kirov, USSR

Sov Med; (8):21-25 1981

Efficacy of active immunotherapy (AIT: nonviable allogeneic leukemic cells, im) was evaluated in 100 acute leukemia patients (52 children and 48 adults). Histologically, 70 had acute lymphoblastic leukemia (ALL) and 30 had acute myeloblastic leukemia (AML). Among these patients, 50 received chemotherapy in combination with AIT and 50 received chemotherapy alone (controls). Rates of remission were 63% and 50%, respectively, in the ALL and AML adults who were administered the combined therapy, compared with 62% and 18% in corresponding controls. The rates were 85% in the ALL children and also 85% in the AML children administered the combined therapy, compared with 74% and 0% in controls. Av durations of survival of the adult ALL and AML patients administered the combined therapy were 22 mo and 9.6 mo, respectively, compared with 11.5 mo and 4.4 mo in controls. Av durations of survival in ALL and AML children administered therapy were 22 mo and 15.4 mo, respectively, compared with 14.8 mo and 6 mo in controls. (8 Refs) (In RUS)

13. PARTIAL NORMALIZATION OF B-CELL FUNCTION BY LEVAMISOLE IN ACUTE LYMPHOBLASTIC LEUKEMIA.

Diez RA, Estevez ME, Sen L
Inst. Investigacious Hematologicas, Academia Nacional de Medicina, Las Heras 3092, Buenos Aires 1425, Argentina
Medicina (B Aires); 41(4):471-475 1981

The functional capacity of B lymphocytes induced by pokeweed mitogen (PWM) to differentiate into plasma cells was investigated in acute lymphoblastic leukemia (ALL) patients in continuous complete remission (CCR) with and without levamisole. Mononuclear cells were obtained from 15-20 ml of blood from each of 14 ALL patient receiving levamisole along with cytotoxic drugs and 7 ALL patients receiving cytotoxic drugs only. Two million cells were treated with rabbit IgG antihuman total immunoglobin conjugated with fluorescein isothiocyanate and examined for surface immunoglobulin. Cells treated with PWM were incubated and examined for cytoplasmic immunoglobulin. Surface antigens were observed in 7.4% of normal patients and 5.4% of ALL patients. Cytoplasmic immunoglobulin in cells cultured with PWM were observed in 4.39% of normal patients, 2.34% of ALL patients receiving chemotherapy plus levamisole, and 0.17% in ALL patients receiving chemotherapy alone. Significantly lower differentiation ability was observed between normal patients and both groups of ALL patients. These results suggest that cytotoxic chemotherapy could induce an intrinsic defect in B cell ability to differentiate or interfere with plasma cell differentiation or regulation, and that levamisole is capable of partly correcting this defect. (18 Refs)

14. INVESTIGATIONAL THERAPY OF HAIRY CELL LEUKEMIA (HCL) WITH THE METHANOL EXTRACTION RESIDUE OF BCG (MER) AND MONONUCLEAR CELL-ENRICHED LEUKOCYTE TRANSFUSIONS (MCT). (MEETING ABSTRACT).

Quesada JR, Hersh EM, Hester J, Verma J, Spitzer G, Keating M, Zander A
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. The Association 187 pp., 1981.

We have investigated whether improvement of hematological parameters can be induced by stimulation of the immune system with MER, knwon to enhance production or release of colony stimulating activity (CSA) and/or normal allogeneic mononuclear cells which provide a cellular source of CSA and may correct the monocyte deficiency found in HCL. Treatment consisted of MER (0.1-0.5 mg/m2 iv weekly) or one to two series of three consecutive MCT alone or concurrently with MER. A complete hematological response (CHR) was defined as: the recovery of a hb above 12 g/dl, neutrophil count above 1500 cells/cumm and platelet count above 1 x 10(5)/cumm. A partial hematological (PHR) response was defined as recovery of at least two of these parameters. Splenectomy had been performed in six patients; all but one of these patients had either progressed or no further benefit could be anticipated. Five patients received MCT resulting in one CHR and two PHR. Two more patients received MCT and MER simultaneously resulting in one PHR. Eight patients were given MER alone, and one patient achieved a PHR. Two of the responsive patients had had no prior splenectomy. Leukemic infiltrate persisted in the bone marrow in all responders, but none has further progressed. Following therapy, the incidence rate was lower in the responder group. MER and MCT induced fever, chills and malaise. Two patients developed skin rashes in association with MCT, and one of them was complicated by pulmonary edema. MCT and MER can induce a hematological response in HCL. The mechanism responsible for this effect is unclear but may be related to enhancement of CSA production and/or favorable cellular interaction between cells from the immune system and the bone marrow. (no Refs)

15. PHASE II TRIAL OF LEUKOCYTE INTERFERON IN CHRONIC LYMPHATIC LEUKEMIA (CLL) (MEETING ABSTRACT).

Mathe G, Gastiaburu J, Goutner A, De Vassal F, Misset JL
ICIG, Inserm U-50, Hopital Paul-Brousse, Villejuif, France
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Nine patients with CLL were treated with sc WBC interferon (Pasteur Institute, Paris). Seven patients received intermittent 10 day courses 1.5M up to 6M units. Four patients received continuous daily administration of 1.5M for three to nine mo (including 2 patients who had previously received intermittent courses). Tumor mass reduction was seen in only 3 patients, but significant decrease in peripheral lymphocytosis was observed in 7 patients, sustained in the continuous treatment group, with relapse at treatment discontinuation in one patient and despite treatment continuation in another patient. Natural killer (NK) cell activity studies revealed a very good correlation between NK activity before and under treatment and clinical response. The patient who experienced a secondary escape under treatment also had a drop in NK cell activity. We conclude that interferon could be useful in CLL and that its clinical activity is correlated with effect on NK cell activity. Further studies are warranted. (no Refs)

16. PHASE II TRIAL OF HUMAN FIBROBLASTIC INTERFERON IN MALIGNANT GAMMAPATHIES AND MENINGEAL LEUKEMIA (MEETING ABSTRACT).

Misset JL, Gastiaburu J, Goutner A, De Vassal F, Mathe G
ICIG, Inserm U-50, Hospital Paul-Brousse, 94800-Villejuif, France
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Eighteen patients (16 myelomas and 2 Waldenstrom's disease) were submitted to a phase II trial of human fibroblastic interferon (RPMI) given iv: 6 million units weekly (Group A: 7 patients) or 3 million units twice weekly (group B: 11 patients). Three patients stopped treatment after 3.3 and 15 infusions for major side effects. Other side-effects were minor and more pronounced in group A. Reduction in M component greater than 50% of initial value was not seen. More than 25 percent was seen in 3 patients. Response became significant only after 3 mo in one patient. Bence Jones proteinuria disappeared in one patient. Bone marrow plasmocytosis decreased greater than 50% in 4 patients and bone pain was significantly decreased in 5 patients. Natural killer (NK) activity studies in these patients did not show clear correlation between level of activity prior or after treatment and response. Patients having meningeal relapse of acute lymphoid leukemia (4 patients) and leukemic lymphosarcoma (1 patient) were given interferon: 1.3 million units daily or qod up to remission or failure. Four patients failed to improve after 5 to 8 injections (and given methotrexate) 1 complete remission was obtained after 11 injections and is still maintained under chemotherapy. Tolerance was good in all cases. NK activity studies were not performed in this five patients. Further studies are warranted in these two clinical situations. (no Refs)

17. A CONTROLLED TRIAL OF CHEMOIMMUNOTHERAPY IN ACUTE MYELOGENOUS LEUKEMIA: A PRELIMINARY ANALYSIS OF A PROSPECTIVE RANDOMIZED COOPERATIVE TRIAL (MEETING ABSTRACT).

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Center for Adult Diseases, Osaka, Japan

Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

After remission induction with DCMP (daunorubicin + cytosine arabinoside (ara-C) + 6-mercaptopurine (6-MP) + prednisolone), patients achieving remission received three courses of consolidation chemotherapy with DCMP and were randomized to receive monthly cycles of maintenance chemotherapy with or without immunotherapy. Immunotherapy consisted of id inoculation of 400ug of the cell-wall skeleton of Nocardia-rubra which was prepared by Prof Y Yamamura, Osaka University, and 10(7) irradiated allogeneic leukemic cells. The study was activated 10-1-78 and will be closed to patient entry 6-30-81. Until the end of October, 1980, 50 patients entered this study. The median remission duration for chemoimmunotherapy was 10 mo compared with 6 mo for chemotherapy alone. Comparable medians for survival were 13 mo and 11 mo respectively. Additional patients and longer follow up will be necessary to determine if the preliminary benefit of chemoimmunotherapy is maintained. (no Refs)

18. THE TRANSFER FACTOR IN THE TREATMENT OF PAPILLOMATOSIS OF THE LARYNX. REPORT OF TWO CASES TREATED IN H.U.C..

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An Otorrinolaringol Iberoam; 8(4):289-294 1981

One patient 6 yr old, had papillomatosis (PL) when he was 3 yr old. He had 18 laryngoscopies (LC) in 6-8 wk intervals. After removal of PL, five units of transfer factor (TF) obtained from a completely cured PL patient, were given at 1 wk intervals. No remission was observed for more than 1 yr. Another patient 11 yr old, had PL 6 yr previously, and underwent 24 LC. Three units of TF from a completely cured condyloma acuminata patient were given to the 11 yr old patient. Removal of papillomas was not necessary during 8 mo. Last LC demonstrated scarce papilloma After TF administration, the patient expectorated papillomatous masses. (4 Refs) (In SPA)

19. COMPARISON OF HUMAN FIBROBLAST AND LEUKOCYTE INTERFERON IN THE TREATMENT OF SEVERE LARYNGEAL PAPILLOMATOSIS IN CHILDREN.

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Eur J Pediatr; 137(2):175-176 1981

Human leukocyte (IFN-alpha) and fibroblast (IFN-beta) interferon were compared in the systemic treatment of two children with recurrent laryngeal papillomatosis. The two patients did not benefit from treatment with iv IFN-beta, but complete control of the disease was achieved by daily sc injections of IFN-alpha. (6 Refs)

20. INTERFERON TREATMENT OF UTERINE CERVICAL PRECANCEROSIS.

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J Cancer Res Clin Oncol; 101(3):303-308 1981

Groups of patients with cervical intraepithelial neoplasia (CIN) were randomly selected for treatment with human leukocyte interferon (13 patients with CIN, Grade I and II) or placebo (18 patients with CIN, Grade I-III). Follow-up studies at 2 yr showed significant differences between the treated and placebo groups with regard to cytologic findings and pathohistological diagnoses. In the controls, the pathologically changed epithelium was persistent in 7/18 cases and there were 7/18 progressions. Among the controls, no regressions were observed. In the patients treated with human leukocyte interferon (HLI), abnormal epithelium persisted in 4/13 cases, progressed in 1/13, and regressed in 8/13. In the control and HLI-treated groups, significant progressions and regressions, respectively were observed in relation to morphogenesis of cervical carcinoma. The differences were greater when the groups were compared. The results indicated that HLI has an impact on the regression of cervical intraepithelial neoplasia. Therapy with HLI is particularly indicated in women in the reproductive age in whom fertility is to be preserved since it may obviate the need for surgery. (10 Refs)

21. INFLUENCE OF HUMAN LEUKOCYTE INTERFERON ON SQUAMOUS CELL CARCINOMA OF UTERINE CERVIX: CLINICAL, HISTOLOGICAL, AND HISTOCHEMICAL OBSERVATIONS. III. COMMUNICATION.

Krusic J, Kirhmajer V, Knezevic M, Ikic D, Maricic Z, Rode B, Jusic D, Soos E

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J Cancer Res Clin Oncol; 101(3):309-315 1981

Fifteen patients (23-55 yr old) with squamous cell carcinoma of the cervix (2 Grade I A, 10 Grade I B, and 3 Grade II B) were treated with human leukocyte interferon (HLI) topically (6 patients: 2 x 10(6) daily units with the contraceptive pessary) alone or with im HLI injections (9 patients: 1 x 10(6) units). HLI was administered for 21 days in 14/15 patients and for 40 days in 1/15. Upons completion of HLI treatment, the patients underwent surgery and/or radiation. After HLI therapy, the tumor regressed 1/3 in size; papillary structures also disappeared from the tumor surface and it was eventually covered by smooth fibrous membrane. At surgery, the peritoneal blood vessels and regional lymph nodes were found to be enlarged. Metastases were observed in only one patient. Would-healing and postoperative course were normal in all 15 patients. No significant difference in response to therapy was noted in patients treated topically and those treated topically and im. Based on stromal response, relationship between tumor cell and macrophage activity, and degree of regional lymph node reactivity, the overall response induced by HLI therapy was considered excellent in 6/15 patients, very good in 5/15, moderate in 1/15, poor in 2/15, and no response in 1/15. Tests made for bacterial antigens showed that the anamnestic immunologic response did not change essentially under the influence of HLI. At 11-34 mo follow-up, no local recurrence or distant metastases were detected in 14/15 patients. (6 Refs)

22. HUMAN LEUKOCYTE INTERFERON IN THERAPY OF PATIENTS WITH URINARY BLADDER PAPILLOMATOSIS, BREAST CANCER, AND MELANOMA.

Maricic Z, Nola P, Ikic D, Smudj K, Oresic V, Knezevac M, Rode B, Jusic D, Soos E
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J Cancer Res Clin Oncol; 101(3):317-323 1981

Patients with malignant recurrent papillomatosis (PMT) of the urinary bladder, breast cancer (BC: 2 primary, 2 recurrent), and recurrent melanoma (RM) of the surgical scar were treated with human leukocyte interferon (HLI). HLI was applied transurethrally by surgical cytoscopy once daily for 21 day in PMT patients. Simultaneously, two PMT patients were given a topical HLI (2 x 10(6)). After a 1-mo interval, HLI was readministered until final tumor regression was achieved. Two patients with diffuse PMT and severe hematuria who could not be treated by the usual therapeutic procedures, im and transurethral HLI allowed papilloma electroresection. After HLI administration, signs of cystitis disappeared, hemorrhaging ceased, and the tumor mass decreased in size. HLI administered after resection brought about complete regression. Cystitis and fibrinous masses present in 8/8 PMT patients gradually disappeared during HLI therapy. Daily for 60 days, BC patients received 2 x 10(6) units HLI intralesionally and 1 x 10(6) im. After 50% regression, the tumor was removed and the patients were given 2 x 10(6) units of HLI, 3 x weekly for 6 mo. No metastasis were observed in the two patients with recurrent BC and only distant metastases were found in 1/2 of those with primary BC. Local recurrence was not found in any of the treated BC patients during the 5-14 follow-up. RM patients received 2 x 10(6) units of HLI daily in the tumor and surrounding tissue until complete regression. The same HLI dose was applied topically for 60 days and im every other day in the one patient with satellite metastases. HLI application decreased tumor size with no signs of local inflammation. In one RM patient there was complete regression and in the other 75% regression. The results showed the antitumoral activity of HLI. (11 Refs)

23. INTERFERON THERAPY IN MULTIPLE MYELOMA: FAILURE OF HUMAN FIBROBLAST INTERFERON ADMINISTRATION TO AFFECT THE COURSE OF LIGHT CHAIN DISEASE.

Billiau A, Bloemmen J, Bogaerts M, Claeys H, Van Damme J, De Ley M, De Somer P, Drochmans A, Heremans H, Kriel A, Schetz J, Tricot G, Vermylen C, Verwilghen R, Waer M
Dept. Human Biology, Rega Inst., K. U. Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium
Eur J Cancer Clin Oncol; 17(8):875-882 1981

Fibroblast interferon at a dosage of 28 x 106U/wk failed to influence disease progression in a preterminal case of therapy-resistant light chain myeloma. In a second case, that had not previously been treated, a first course of fibroblast interferon (30 x 106U/wk) associated with corticosteroids remained without effect. In this patient subsequent leukocyte interferon treatment was associated with a decrease in urinary light chain excretion and normalization of calcemia, all other parameters remaining unaltered. A third patient with light chain disease was resistant to chemotherapy ab origine. None of the disease parameters responded to either fibroblast or leukocyte interferon therapy (21 x 106U/wk). During therapy a downward trend occurred in the relative number of lymphocytes characterizable as B and T cells. Mitogenic reactivity remained unchanged except for a downward trend, during fibroblast interferon therapy, in reactivity to PHA and Con A after 6 days culturing. Spontaneous (background) mitogenesis upon culture showed an upward trend. (Author abstract) (26 Refs)

24. EFFECTIVENESS OF POSTOPERATIVE ADJUVANT THERAPY WITH CYTOTOXIC CHEMOTHERAPY (CYTOSINE ARABINOSIDE, MITOMYCIN C, 5-FLUOROURACIL) OR IMMUNOTHERAPY (NEURAMINIDASE-MODIFIED ALLOGENEIC CELLS) IN THE PREVENTION OF RECURRENCE OF DUKE'S B AND C COLON CANCER.

Rainer H, Kovats E, Lehmann HG, Micksche M, Rauhs R, Sedlacek HH, Seidl W, Schemper M, Schiessel R, Schweiger B, Wunderlich M

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Recent Results Cancer Res; 79:41-47 1981

Preliminary evidence on the effectiveness of adjuvant chemotherapy or immunotherapy in 81 patients with adenocarcinoma of the colon is reported. All patients had undergone apparently complete tumor resection and were classified as Duke's class B, C1, or C2. Chemotherapy consisted of 100 mg cytosine arabinoside on day 1 and 2 mg mitomycin and 12 mg/kg 5-fluorouracil (x3) on days 1 and 2. Treatment was repeated 3x at 6-wk intervals if hematologic recovery had occurred. Immunotherapy involved sc injection of allogeneic colon cancer cells modified with various concentrations of neuraminidase according to a 'chessboard' vaccination method. Enzyme and cells were admixed without preincubation or washings. Recurrent tumor was found in four controls, and two chemotherapy and two immunotherapy patients. Immunotherapy patients had the longest disease-free interval. Class C patients showed lower reactivity to vaccinations than Class B patients. Response to tumor cells was apparently boosted by exposure to neuraminidase-treated cells. Preliminary results suggest some prognostic and therapeutic value for the chessboard vaccination method. (4 Refs)

25. EFFICACY OF BCG ADJUVANT THERAPY IN BREAST CANCER (MEETING ABSTRACT).

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Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Following loco-regional treatment (radiotherapy and surgery), one hundred breast cancer patients (T1-T3: No-N1b) were randomized in two groups: 1) no adjunct treatment or 2) 150 mg Immun BCG-F (Pasteur Institute) po, once a wk for 1 yr. The study has since ended and all patients have been followed for at least 20 mo. No side effects were observed for BCG (vomiting, diarrhea...) necessitating cessation of treatment. After 35 mo, the BCG group shows 20% relapse and no mortality compared to 54% relapse in the control group and 2 deaths. Moreover, the BCG group demonstrated a significant immunorestoration: delayed hypersensitivity skin tests; level of circulating auto-rosette forming cells; natural killer (NK) activity and anti BCG antibodies. These results confirm that cancer patients in whom immunity was restored to normal levels, have a improved prognosis. (no Refs)

26. LEUKOCYTE INTERFERON-INDUCED TUMOR REGRESSION IN HUMAN METASTATIC MALIGNANT DISEASE RESISTANT TO CHEMOTHERAPY (MEETING ABSTRACT).

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Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

A phase II study with partially purified WBC interferon obtained by Contell technique, modified by Soos (using Contell strain Sendai virus) has been carried out in 42 patients with adv anced cancer (breast, lung adenocarcinoma, gastric, prostatic, melanoma and multiple myeloma. Patients were treated by im injections of 3 x 10(6) IU/m2, in periods of 3 to 5 days every 2 wk during 6 mo. Complete clinical response was obtained in the following cases: cancer of breast: 1 out of 9, prostata: 1 out of 6, melanoma: 1 out of 6, multiple myeloma: 2 out of 6 cases. Tumor regression was observed in the following cases: cancer of breast: 4 out of 8, lung: 4 out of 8, stomach: 4 out of 7, prostata: 3 out of 6, melanoma: 2 out of 6, multiple myeloma: 3 out of 6 cases. Circulating interferon level 4 hr after the injection was in the range of 30 to 50 IU/ml of plasma. Side effects included febrile reactions (usually 2-4 hr after injection), malaise and asthenia to a varying degree. In one patient reversible thrombopenia (60,000) and leukopenia (2,200) were observed. No side effects were observed with regard to cardiac, renal and hepatic functions, which were carefully monitored. (no Refs)

27. CLINICAL EXPERIENCES WITH HUMAN FIBROBLAST INTERFERON (MEETING ABSTRACT).

Furue H, Komitu T, Kobayashi H, Hakozaki M, Kondo S, Tajima S

Teikyo University, Tokyo, Japan

Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

From our clinical observations, human fibroblast interferon (IF) was rapidly cleared from the circulation of cancer patients. The early half time was twenty min in one shot iv administration and sixty min in drip infusion. IF was not detected beyond six hr after administration. On the contrary, IF was never detected in the serum throughout a period of 24 hr observation following im injection. Seventeen cases with advanced cancer (acute myelogenous leukemia (AML) 4, monocytic leukemia (Mol) 1, malignant lymphoma 4, multiple myeloma 1, solid cancer 7) have now received iv injection of human fibroblast. IF. The doses have ranged between one and three million units daily or two to three x weekly. Some patients have received IF therapy for more than three mo. One case of AML, a five yr-old girl, completely recovered from her moribund state after total dose of 3.1 x 10(6)/kg units of IF treatment. Another two cases of AML who received combination of chemotherapy and IF, complete remission was also observed. However, immunological parameters (lymphocyte number, T-cell % and number, B-cell % and number, phytohemagglutinin blastogenesis, and IAP-immunosuppressive acid protein-levels etc) did not show significant improvement in single administration of IF. Preliminary results obtained with human fibroblast IF treatment in cancer patients argues for the increase of therapeutic trials. More laboratory and clinical studies in man are warranted. (no Refs)

28. IMMUNOLOGICAL MECHANISM OF DISAPPEARING ASCITES IN CANCER PATIENTS FOLLOWING INT RAPERTITONEAL ADMINISTRATION OF A STREPTOCOCCAL PREPARATION, OK-432 (MEETING ABSTRACT).

Katano M, Nomoto K, Torisu M
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Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Seventy-seven patients with ascites caused by the cancer of the digestive tract were treated by ip injection of OK-432, penicillin-and heat-treated lyophilized powder of Su-strain of streptococcus pyogens A3. Complete disappearance of effusion was observed in 43 cases, it caused reduction in 5 out of 77. In addition, the mean survival time of these 48 responsive cases showed a significant prolongation (13.1 mo), compared with that of 23 palliative cases (2.6 mo). We studied on the morphological and functional relationship between host's inflammatory cells and tumor cells in ascites after the ip injection of OK-432. After OK-432 injection, neutrophils, macrophages and lymphocytes increased in number in ascitic fluid. The absolute number of tumor cells decreased with the increasing number of host's inflammatory cells. Increased lymphocytes were mainly T-cells. About half of these T-cells were activated T-cells. Increased macrophages were in an activated state. OK-432-induced neutrophils, lymphocytes, probably activated T-cells, activated macrophages and OK-432 itself inhibited DNA synthesis of patient's ascites-derived tumor cells in vitro. These results indicate that OK-432-induced host's inflammatory cells and OK-432 itself may play an important role in tumor cell destruction and disappearance of ascites. (no Refs)

29. PROPHYLACTIC HUMAN LEUKOCYTE INTERFERON AFTER ALLOGENEIC MARROW TRANSPLANT (MEETING ABSTRACT).

Meyers JD, Neiman PE, Thomas ED
Fred Hutchinson Cancer Research Center, Seattle, WA
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Prophylactic human WBC interferon (HLI) may be useful in preventing both cytomegalovirus (CMV) infection and leukemic relapse, which are two of the major complications of allogeneic marrow transplantation for leukemia. Though marrow toxicity may interfere with its use in such patients, we have previously found daily doses up to 1.6 x 10(5) units/kg/day to be well-tolerated. We have therefore initiated a randomized study of prophylactic HLI given after allogeneic marrow transplant for acute lymphocytic leukemia in remission. HLI is given every 3 days from approx day 18 after transplant through day 80. Starting dose is 6 x 10(4) units/kg and doses of 7-12 x 10(4) units/kg have been tolerated by most patients. HLI recipients have significantly lower circulating neutrophil counts than do control patients and HLI doses are a djusted to keep the nadir of the circulating neutrophil count greater than 500/cu mm. Other side-effects have included fever and significant anorexia. Recipients have 20-30% higher natural killer (NK) activity against K562 cells compared with control patients. Further augmentation of NK activity by in vitro incubation of cells with HLI is blunted. Thus it appears that NK activity is maximally stimulated at the doses being used. Thirty patients have entered the study to date, 16 as control patients and 14 who have received HLI. Two leukemic relapses have occurred in each group, though the two HLI recipients had received doses of HLI lower than those described above during the initial toxicity trials. Two cases of CMV pneumonia have occurred among control patients and one case among HLI recipients. Thus, the clinical efficacy of prophylactic HLI in this patient group remains to be determined. (no Refs)

30. CONSIDERATIONS ABOUT THE USE OF LEVAMISOLE IN PATIENTS AFFECTED BY PRIMARY CANCER.

Marzo C, Grasso P, Gennarelli E, Vitiello N, Borrelli G, Pasquinucci S, Antropoli L
Istituto di Clinica Tisiologica, I Facolta di Medicina e Chirurgia dell'Universita degli Studi di Napoli, Napoli, Italy
Rass Int Clin Ter; 61(5):289-293 1981

This study was undertaken to elucidate some aspects of levamisole (Le) effect on primary lung cancer. Advantageous and undesirable side effects were studied. All 51 patients with lung cancer diagnosis had tests in vivo for recall antigen (paraphenylenediamine - PPD), and in vitro for rosettes (E, EA, EAC), and lymphocyte blast (phytohemagglutinin - PHA). These tests were repeated every 21-28 days. There was not always agreement between tests in vivo and in vitro. Patients were treated by surgery, irradiation, and cytostatic therapy. Le therapy was started when percent of lymphocytes forming rosettes E in vitro was less than 50%, even in cases when PPD was highly positive (ie giving normal reaction). Of the 51 patients 16 were immuno depressed at the time of diagnosis. All 16 patients received Le therapy. Another seven became immuno depressed later (5 after cytostatic therapy, which did not change PPD results). In all 23 patients, Le therapy caused almost immediate return to normal for rosette forming lymphocyte numbers. Patients showing reduction of lymphocytes T and decrease in tuberculine sensitivity, after Le therapy, demonstrated increase in T lymphocytes and no change in tuberculine (contrary to other published data). Le therapy did not show any side effects. Possible explanation of these results was offered. (11 Refs) (In ITA)

SYNTHETIC IMMUNOTHERAPEUTIC AGENTS

31. INEFFECTIVENESS OF LEVAMISOLE AS ADJUVANT TO SURGERY WITH TWO LINES OF TRANSPLANTED RAT COLONIC CARCINOMA.

Martin MS, Justrabo E, Martin F, Michel MF, Leclerc A
Lab. Immunology, INSERM U.45 CNRS ERA628, Dijon, France
Br J Cancer; 44(3):464-466 1981

The efficacy of adjuvant chemotherapy with levamisole (LM) was studied in BDIX rats with sc transplanted intestinal adenocarcinomas induced by 1,2-dimethylhydrazine in syngeneic rats. Animals were subjected to a partial or curative excision of the tumor; 8 days after surgery rats were given repeated ip injections of LM (2.5 mg/kg/wk). LM administration did not prevent lung or mediastinal metastases. There was no significant difference between LM-treated and control rats in survival rates or the incidence of local recurrences. (13 Refs)

32. BLOOD GROUPS AND THE RESPONSE TO IMMUNOTHERAPY.

Anthony HM
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Cancer Immunol Immunother; 11(4):287-289 1981

Lung cancer was treated in 217 cases by resection followed by immunotherapy with levamisole or a placebo. Patients with O group or Rh- blood showed poorer survival when treated with levamisole than all other patients. The lower survival rate was apparent even after an allowance had been made for extent of disease and deaths in the 6 wk after surgery excluded. Most patients dying during the first 6 postoperative wk had confirmed or suspected recurrent tumor. Five patients, including four group O and one Rh-, died of cardiac failure. Among 98 patients receiving palliative treatment, levamisole-treated Rh- patients showed a poorer survival rate than placebo-treated and Rh+ patients, but O group patients showed the same survival rate as the rest of the palliative group. The Rh- and groups apparently are more susceptible to autoimmune disease affecting the cardiorespiratory system. Rh- and O patients appear to be affected by different mechanisms. Trauma of surgery evidently is a factor among the O group, since palliative therapy with a lower degree of trauma is not accompanied by decreased survival rate. The effect of blood grouping on response to therapy has implications for planning and interpretation of immunotherapy trials. (11 Refs)

INTERFERON

33. BONE MARROW STEM CELL REGULATION IN VITRO BY INTERFERON (IF) AND ANTI-INTERFERON (ANTI-IF) IN NORMAL SUBJECTS AND IN MALIGNANT LYMPHOMA PATIENTS (MEETING ABSTRACT).

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Exp Hematol; 9(Suppl9):157 1981

The purpose of this investigation is to evaluate the effect of human WBC IF, type I, and of anti-IF immunoglobulins on the hemopoietic progenitors in vitro in normal subjects and in lymphoproliferative disorders. We have studied the in vitro effects of human IF on growth of human granulocyte-macrophage (CFU-C) and lymphocyte (CFU-L) progenitors of normal donors and malignant hemopoietic cells from lymphoproliferative disorders. In several experiments we have tested the dose-response effect of human IF and its inhibition by anti-IF immunoglobulins. We observed that the IF inhibits the colonies growth of normal donors at doses greater than or equal to greater than than 1000 U for each culture system. Secondly we investigated if there is any difference in the CFU-C, CFU-L value between normal subjects and malignant lymphoma patients and if IF can have a different inhibitory effect in the two experimental groups. In this second group of experiments we demonstrated that the IF causes a significant reduction in the ability of bone marrow cells to form colonies in vitro (CFU-C, CFU-L) in both groups. However our results show that the IF exerts a similar inhibitory effect both on the granulocyte-macrophage and T-lymphocyte colonies, but we observed a significant decrease in the value of the colonies (CFU-C, CFU-L) in the malignant lymphoproliferative bone marrow disorders as compared with control bone marrow. The results suggest a different sensitivity to IF between normal and malignant cells populations. (no Refs)

34. THE EFFECT OF ALPHA-INTERFERON ON THE NATURAL KILLER- AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY OF MALIGNANT AND NON-MALIGNANT LYMPHOCYTE SUBSETS IN CHRONIC LEUKEMIA (MEETING ABSTRACT).

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Department of Medicine and Haematology, University of Aarhus, Aarhus, Denmark
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Malignant and non-malignant lymphocyte subsets from untreated B-chronic lymphocytic leukemia (CLL) patients were isolated by sequential rosette sedimentation procedures and tested, together with unfractionated lymphocytes, in the natural killer (NK) and antibody-dependent cellular cytotoxicity (ADCC) assays. Though addition of alpha-interferon (alpha-IFN) enhanced the NK potential in all patients, unfractionated lymphocytes alone exhibited grossly defective capacities in both assays, when compared to normal donors. Whereas the malignant mouse rosette forming cells were devoid of both NK and ADCC function, the non-malignant T cells, though by themselves deficient in NK function, could be boosted to subnormal levels by addition of alpha-interferon. Likewise, a negatively selected Null cell fraction was also shown to exhibit considerable NK and ADCC function. Addition of alpha-IFN to ADCC cultures had no effect on the amount of lysis. NK experiments with a panel of target cells with different NK sensitivities showed that B-CLL patients after the addition of alpha-IFN were able to lyse even the resistant DAUDI cell line. These findings, which suggest a strong regulatory role of alpha-IFN on the NK function of non-malignant lymphocytes in CLL, are discussed in relation to our present knowledge concerning NK cells in normal donors. (no Refs)

35. INTERFERON-INDUCED AUGMENTATION OF NATURAL KILLER CELL ACTIVITY BY SPLENOCYTES FROM LEUKEMIA VIRUS IMMUNOSUPPRESSED MICE (MEETING ABSTRACT).

Bendinelli M, Cox WI, Specter S, Friedman H
Department of Microbiology, University of Pisa, Pisa, Italy
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Friend leukemia virus (FLV) infected mice show a marked deficiency in a wide variety of immune functions. In the present study, the natural killer (NK) cell activity of splenocytes from FLV-infected mice was examined in vitro and the effects of fibroblast interferon (IFN beta) on such cells was determined. Whereas splenocytes from normal BALB/c mice were found to express natural cytolytic activity against target cells such as the chromium-51 labelled YAC-1 cell line, similar preparations of spleen cells from BALB/c mice at various times after infection with FLV showed markedly reduced NK activity within 4-6 days after FLV infection prior to development of overt symptoms of leukemia, there was a 20-40% suppression of NK activity as compared to control mice. By 10-15 days after infection, NK activity was decreased by 70-80% of control values. Similar to cells from control animals, preincubation of spleen cells from FLV-infected mice with relatively small amounts of IFN beta increased the NK activity approx 2-fold, though the absolute level of NK activity was still markedly depressed. When spleen cells from FLV-infected mice or a continuous cell line of FLV-induced leukemic cells (GM 979) were labelled with chromium and used as targets, no cytolysis occurred upon exposure to normal splenocytes indicating these cells are resistant to such lysis. However, following 4 days of treatment of GM 979 with dimethylsulfoxide in vitro, the cells differentiated into hb secreting cells which then were susceptible to NK mediated cytolysis by normal splenocytes. IFN beta augmented the NK activity against the differentiated GM 979 but did not bring about killing of undifferentiated GM 979. (no Refs)

36. IMMUNOLOGICAL STUDIES IN CHRONIC LYMPHOCYTIC LEUKEMIA. II. NATURAL KILLER- AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY POTENTIALS OF MALIGNANT AND NON-MALIGNANT LYMPHOCYTE SUBSETS AND THE EFFECT OF ALPHA-INTERFERON.

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Med. afd. II, Aarhus Amtssygehus, 8000 Aarhus C, Denmark
Leuk Res; 5(4/5):349-355 1981

The effector cell potential of chronic lymphocytic leukemia (CLL) subsets was determined in the natural killer (NK) and antibody-dependent cellular cytotoxicity (ADCC) assays. Lymphocyte subpopulations were isolated from peripheral blood obtained from 25 (43-76 yr old) CLL patients. The behavior of CLL cells in NK and ADCC assays was determined. Basic experimental conditions for the assays wer e determined. When unseparated lymphocytes from CLL patients were tested in NK (21 patients) and ADCC (25 patients) assays and compared to the cytotoxicities of 20 normal donors, the CLL cells were defective in both tests. The behavior of CLL cells in NK assays was defective with or without 1,000 IU alpha-interferon (AIF). The NK and ADCC defects were found mainly in the non-T fraction, while the T cells exhibited subnormal levels of lysis. By depleting the non-T cells of mouse rosette forming cells, a null cell subset was purified that exhibited considerable lysis in the NK test. AIF did not enhance ADCC by unfractionated CLL cells. When the NK activity of three CLL patients were tested against 7 target cell lines with NK sensitivities in normal donors ranging from very low to extremely, the same pattern was retained in the patients, although the addition of AIF tended to diminish the tendency by boosting the NK activity against the resistant lines proportionately more than against the sensitive ones. Compared with lysis by cells from normal donors, the lysis of cells from the patients, was still defective with all cell lines tested. (19 Refs)

37. ENHANCING EFFECT OF INTERFERON (IF) ON THE INDUCTION OF KILLER T CELLS AGAINST ASCITES HEPATOMA (MH134) (MEETING ABSTRACT).

Unoura M, Hatano M, Kato Y, Kobayashi K, Hattori N
Dept. Virology, Cancer Res. Inst. Kanazawa Univ., Kanazawa-shi, Ishikawa Pref. 921, Japan
Proceedings of the 17th Annual Meeting of Japan Society of Hepatology held in Gifu, Japan, 25-26 June, 1981. Japan Society of Hepatology, Tokyo 113, Japan, 148 pp., 1981.

As in vivo treatment, female C3H/He mice, 8-to 12-wk-old at the beginning of the experiment, were left untreated (Group I), or given 2 x 10(4) unit of IF ip (Group II), 1 x 10(6) mitomycin C (MMC)-treated MH134 cells (derived from C3H/He mice) ip (Group III) or 2 x 10(4) unit of IF + 1 x 10(6) MMC-treated MH134 cells (Group IV). After 10 days of these treatments, the spleen cells of the mice were cultured alone (a), with MMC-treated MH134 cells (b), or with IF + MMC-treated MH134 cells (c) in vitro for 5 days. For the MMC treatment, 1 x 10(6) MH134 cells were treated with 100 ug of MMC for 45 min, and for the IF treatment, 1 x 10(6) MH134 cells were treated with 2 x 10(4) unit of IF for 2 hr. The cytotoxicity determined by 51Cr-release assay (effector, mouse spleen cells; target cells, MH134; effector/target ratio 40/1) during a 16-hr period after 5 days of in vitro culture which was begun 10 days after in vivo treatment for (a), (b) and (c), respectively, was 0%, 0% and 8.0%, in Group I; 13.6%, 22.8% and 19.3%, in Group II; 20.2%, 29.0% and 28.9% in Group III, and 48.4%, 40.3% and 56.7% in Group IV. When the spleen cells of the mice treated in the same way as c in Group IV were treated with anti-theta-antibody (theta) and complement (C), the cytotoxicity was 0% while it was 39.6% without the theta or C treatment and 34.9% with the C treatment alone. From the results of (a) in Groups I and II, IF was thought to augment the nonspecific cytotoxicity, and from those of (b) and (c) in Groups I and II, the recognizing potential of syngeneic tumors was thought to be augmented in the spleen cells of the mice given IF, and the tumors treated with IF to be more easily recognized. The results of (a) in Groups I, III and IV showed that when only a primary stimulus is given in vivo or when the secondary stimulus is given in vitro, the IF + MMC-treated MH134 tumor is most easily recognized. The effector in (c) in Group IV was shown to be the T cells. (no Refs) (In JPN)

38. REGRESSION OF VIRAL-INDUCED TUMORS BY RETINOID AND INTERFERON (MEETING ABSTRACT).

Frankel JW, Horton EJ, Ito Y

Department of Health and Rehabilitative Services, Tampa, FL

Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

We presented evidence that prophylactic treatment of hamsters and chickens with aromatic retinoid Ro 10-9359 (ethyl all-trans-9-(4-methoxy-2, 3, 6-trimethylphenyl)-3, 7-dimethyl-2, 4, 6, 8-nonatetraenoate), that possesses a favorable therapeutic index, results in inhibition of Rous sarcoma virus (RSV) tumorigenesis. Therapeutically administered, the retinoid causes slight reduction in overall tumor size. We now report marked therapeutic effects by combination of retinoid (50 mg/kg) and chicken embryo fibroblast interferon (100 units) against RSV-induced tumors in chickens in terms of regression and/or confinement of the tumor to the primary site. IM injections are initiated when all chickens develop palpable wing-web tumors, and at weekly intervals thereafter. Forty-nine days after the first injection, tumor regression (50% or greater reduction in tumor size) is noted in 83% of chickens receiving both retinoid and interferon, compared with 28%, 33% and 3% of chickens inoculated with retinoid, interferon and peanut oil diluent, respectively. Similar relationships are observed relative to tumor confinement at the primary wing-web site. The sensitivity of RSV-induced tumors to therapeutic retinoid plus interferon treatment warrants further study of Ro 10-9359 and other retinoids combined with interferon and other oncogenic viruses and animal models. (no Refs)

39. INTERFERON ACTS DIRECTLY ON HUMAN B LYMPHOCYTES TO MODULATE IMMUNOGLOBULIN SYNTHESIS.

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J Immunol; 127(5):2146-2150 1981

At different times of exposure, interferon (IFN) enhanced and suppressed pokeweed mitogen- (PWM) induced IgG synthesis by human peripheral blood lymphocytes (PBL). Pretreatment of PBL with IFN frequently increased antibody production by more than 100% when compared with that by untreated PBL. Results of experiments in which PBL were separated into T and B subpopulations indicated that IFN preparations acted directly on B cells. Thus, mixtures of IFN-treated B cells and untreated T cells from five of seven persons tested produced 81% to 500% more IgG than untreated, matched control cells. However, IFN-treated monocytes mixed with untreated B and T cells or IFN-treated T cells mixed with untreated B cells failed to enhance IgG production significantly in similar assays. In contrast to the pretreatment protocol, when IFN was present in the incubation mixture throughout the PWM assay, IgG production decreased. Sephadex chromatography of the IFN and tests of the resulting fractions indicated that the IgG production-enhancing activity was located in the fraction carrying the antiviral activity. (Author abstract) (33 Refs)

40. EFFECT OF HUMAN LEUKOCYTE INTERFERON ON HUMAN LYMPHOCYTES IN VITRO: CYTOGENETIC STUDIES.

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Sect. Hematology, Aalborg Hosp., 9000 Aalborg, Denmark

Mutat Res; 90(2):143-147 1981

In vitro effects of interferon (IF) on chromosomal stability in mitogen-stimulated peripheral blood lymphocytes from normal individuals were investigated. Although no increase in structural chromosome aberrations was found, the response of lymphocytes to various mitogens was inhibited by IF. (21 Refs)

41. COMPARATIVE STUDY OF ANTIVIRAL AND ANTIPROLIFERATIVE ACTIVITIES OF HUMAN INTERFERON ISOLATED FROM SUSPENSION AND STATIONARY CULTURES OF DONOR LEUKOCYTES.

Timofeev IV, Kuznetsov VP, Mekhedov LN, Nikolaeva TG, Orlova TG, Dobrynin IaV

N. F. Gamaleia Inst. Epidemiology and Microbiology, All-Union Cancer Res. Center, Moscow, USSR

Antibiotiki; 26(9):703-705 1981

Human interferons (IFs) isolated from the suspension cultures (IF-1) and stationary cultures (IF-2) of donor WBC showed comparable inhibitions of proliferative activity in CaOv cells. The antiviral activity of the IF-2 was lower than that of the IF-1. (8 Refs) (In RUS)

42. PHYSICOCHEMICAL AND ANTIGENIC PROPERTIES OF SYNTHETIC FRAGMENTS OF HUMAN LEUKOCYTE INTERFERON.

Arnheiter H, Thomas RM, Leist T, Fountoulakis M, Gutte B
Lab. Molecular Genetics, Natl. Inst. Neurological and Commmunicative Disorders and Stroke, NIH, Bethesda, MD, 20205
Nature; 294(5838):278-280 1981

In view of the fact that conservation of segments of polypeptide chains during evolution may indicate their functional importance, three carboxyl-terminal fragments of human interferon-alpha1 (IHNa1) ranging in size from 33-96 amino acid residues were synthesized. The three fragments were synthesized by the solid-phase method. None of the fragments exhibited antiviral activity. Further experimental details are given for the 56-residue fragment because antibodies previously have only been raised against it. Three BALB/c mice were immunized against the 56-residue fragment, their spleen cells pooled and fused to cells of mouse myeloma line Fo, and hybrid cells selected for production of fragment-binding antibodies. The monoclonal antibody so produced bound intact IFN-a1 and human WBC interferon-alpha2 without neutralizing their antiviral effect. Thus, this antibody, directed against a largely conserved region, may show substantial cross-reactivity within the interferon protein family. (22 Refs)

43. INVOLVEMENT OF A RADIORESISTANT CELL IN THE PRODUCTION OF CIRCULATING INTERFERON INDUCED BY NOCARDIA FRACTIONS IN MICE.

Barot-Ciorbaru R, Catinot L, Wietzerbin J, Petit JF, Chedid L, Falcoff E
Institut de Biochimie, Universite Paris-Sud, Bat. 432, 91405 Orsay, France
J Reticuloendothel Soc; 30(4):247-257 1981

Circulating interferon induction by the immunostimulant Nocardia fractions Nocardia water soluble mitogen (NWSM), Nocardia water soluble mitogen pellet (NWSMP) and peptidoglycan was studied in nude and irradiated mice. The three fractions were active in nude mice, suggesting that cells of thymic origin are not required for interferon synthesis induced by these fractions. NWSM and NWSMP were capable of interferon induction in irradiated mice, but peptidoglycan was inactive. Interferon titers induced by NWSM and NWSMP in irradiated mice were similar to those obtained in normal mice. these results indicate that the cell population (probably macrophages), involved in NWSM- and NWSMP-induced interferon production was radioresistant, whereas the presence of a radiosensitive cell population (probably lymphocytes) was necessary for interferon synthesis induced by peptidoglycan. The antigenic properties and pH stability of interferon induced by the different Nocardia fractions in nude and irradiated mice were examined. The interferon induced by peptidoglycan in nude mice appeared to be related to Type II (now called gamma) interferon. NWSMP, which induced a Type I interferon in normal and nude mice, had the same activity in irradiated mice. NWSM, which contains both NWSMP and peptidoglycan, induced Type I interferon in irradiated mice. NWSM and NWSMP were active interferon inducers in several mouse strains, including endotoxin-resistant C3H/HeJ mice. (Author abstract) (41 Refs)

44. BINDING OF 125I-LABELLED HUMAN ALPHAINTERFERON TO HUMAN LYMPHOID CELLS.

Mogensen KE, Bandu MT, Vignaux F, Aguet M, Gresser I
Institut de Recherches Scientifiques sur le Cancer, Laboratoire d'Oncologie Virale, BP 8, 94802 Villejuif Cedex, France
Int J Cancer; 28(5):575-582 1981

To investigate the binding of interferon to human lymphoid cells, we purified human alpha interferon and radio-labelled it with iodine-125. Binding at 4 C could be saturated and was inhibited by unlabeled interferon; it was specific for cells of human origin. Dissociation constants for the complex of interferon and receptor site were of the order 10(-9) -10(-11) M. All human cells tested showed such binding. Occupation of these high-affinity sites, at 37 C, was compared with the inhibition of cellular growth due to interferon. The most sensitive cell line (Daudi) gave a complete biological response with only a fraction of its sites occupied. Evidence of two sites was found for a line (P3HRI) showing intermediate sensitivity. A relatively insensitive line (Raji) showed no response when all its high-affinity sites were occupied. (Author abstract) (38 Refs)

45. SPECIFIC HIGH-AFFINITY BINDING OF 125I-LABELED MOUSE INTERFERON TO INTERFERON RESISTANT EMBRYONAL CARCINOMA CELLS IN VITRO.

Aguet M, Gresser I, Hovanessian AG, Bandu MT, Blanchard B, Blangy D
(c/o Gresser) Lab. Viral Oncology, Institut de Recherches Scientifiques sur le Cancer, BP 8, 94802 Villejuif, France
Virology; 114(2):585-588 1981

Multipotential mouse embryonal carcinoma cells are resistant to several biologic effects of mouse interferon: inhibition of viral multiplication and inhibition of cell division. Nevertheless using 125I-labeled highly purified mouse interferon we have shown that these embryonal carcinoma cells express specific interferon receptors in similar number and of the same affinity as interferon sensitive differentiated embryonal carcinoma cells. Thus, mechanisms of interferon resistance are probably multiple: some cells are resistant because they lack specific binding sites for interferon (interferon resistant mouse L1210 cells) and other cells, as shown herein, are resistant to some of the effects of interferon despite binding of interferon to specific receptor sites. Furthermore, these binding sites may be considered functional, since interferon does induce an increase in 2-5A synthetase in these cells. (Author abstract) (9 Refs)

46. REGULATION OF HUMAN NATURAL KILLING. I. THE ROLE OF MONOCYTES, INTERFERON, AND PROSTAGLANDINS.

Koren HS, Anderson SJ, Fischer DG, Copeland CS, Jensen PJ
Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27110
J Immunol; 127(5):2007-2013 1981

We have found that human endogenous natural killer activity as measured in a rapid 51Cr release assay is unaffected by the presence of monocytes. Moreover, stimulation of natural killer cells by poly I:C is independent of monocytes. In contrast, the presence of monocytes in a mixed population of mononuclear cells that have been stimulated by poly I:C suppresses NK activity. The suppression is shown to be partially reversible if indomethacin (10(-6) M) is added to the cultures during stimulation. Culture supernatants of monocytes stimulated with poly I:C are shown to contain PGE1 in a radioimmunoassay, and have NK inhibitory activity comparable to that obtained with exogenous PGE1 added to NK assays at a concentration range of 10(-7) to 10(-9) M. Culture supernatants from poly I:C-stimulated monocytes do not have detectable levels of antiviral activity. In contrast, plastic nonadherent cells stimulated with poly I:C produce significant levels of interferon (100 to 200 U/ml/2 x 10(6) cells) but almost undetectable amounts of PGE. Supernatants of nonadherent cells incubated with indomethacin (10(-6) M) alone augment NK activity. Taken together, the results suggest that stimulation of mononuclear cells with poly I:C is dependent on and regulated by the relative levels of interferon produced by lymphocytes and PGE produced by monocytes. (Author abstract) (52 Refs)

INTERFERON INDUCING AGENTS

47. IMMUNE INTERFERON INDUCTION BY A MONOCLONAL ANTIBODY SPECIFIC FOR HUMAN T CELLS.

Pang RH, Yip YK, Vilcek J
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Cell Immunol; 64(2):304-311 1981

OKT3, a monoclonal antibody reactive with a surface antigen shared by all human T lymphocytes, was found to act as a potent interferon (IFN) inducer in cultures of human mononuclear WBC. Two other monoclonal antibodies reactive with T-cell subpopulations failed to induce IFN. IFN-inducing activity of OKT3 was similar to that of phytohemagglutinin (PHA). The phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA) had a strong potentiating effect on IFN production stimulated with OKT3 or PHA. IFN produced after stimulation with OKT3, like PHA-induced IFN, had properties characteristic for 'immune' IFN (IFN-gamma). (Author abstract) (26 Refs)

48. INTERFERON INDUCERS AS ANTIVIRAL AND ANTINEOPLASTIC AGENTS (MEETING ABSTRACT).

Stringfellow DA, Weed SD
Experimental Biology Research, The Upjohn Company, Kalamazoo, MI, 49001
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

We recently reported that a series of 5-halo-6-aryl-pyrimidinones were active interferon-inducing antiviral agents. In this report we compare the biologic activity of selected members of this series of compounds with several well known interferon inducers. Compounds were compared on ability to induce interferon and protect mice from lethal Semliki Forest or type 1 herpes simplex virus infection and their antitumor activity in mice injected with B16 malignant melanoma cells. A direct correlation was found between the relative magnitude and duration of antiviral and antitumor activity. There was not, however, a uniform correlation between antiviral or antitumor activity and magnitude of the interferon response. Some of the poorest inducers had the best antiviral-antitumor activity. The pyrimidinones reduced metastasis of B16 malignant melanoma cells injected iv or following surgical removal of a primary, sc implanted tumor. The antitumor and antiviral activity of the pyrimidinones appeared to be mediated by several factors including enhancement of interferon independent host defenses and physical parameters affecting tumor development and metastasis. (no Refs)

49. INDUCTION OF INTERFERON AND NK ACTIVITY BY A NOVEL ORGANOGERMANIUM COMPOUND, GE-132 (MEETING ABSTRACT).

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Department of Bacteriology, Tohoku University School of Medicine, Sendai, Japan

Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Ge-132 (carboxyethylgermanium sesquioxide) is a novel organogermanium compound synthesized in the Asai Germanium Institute, Tokyo, Japan, in 1967. Toxicological and pharmacokinetics studies have revealed that Ge-132 is of extremely low toxicity and has several unique physiological activities, which include marked antitumor and antihypertension. And also this compound has been developed as immunopotentiating agents, which induced interferon (IFN) and augumented natural killer (NK) activity. In the present study we demonstrated that Ge-132 induced IFN and augumented NK activity. A microplate 50% plaque reduction assay for IFN and a 51Cr-release method for NK activity were performed. In mice after oral administration of Ge-132 (100 mg/Kg) a significant level of IFN activity appeared in a serum by 16 hr and reached a peak of 320 u/ml at 24 hr. This IFN was inactivated by treatment with acid (pH 2.0) and by incubation at 56 C. NK activity of spleen cells was augumented by 12 hr and reached a peak at 24 after the administration. In human NK activity was augumented by 6 hr and reached a peak at 24 hr after oral administration. IFN in a serum was also detected after the administration. Finally we have confirmed that Ge-132 induces IFN and augments NK activity in both mice and humans. (no Refs)

50. BACK OF INTERFERON INDUCTION BY POLYADENYLIC-POLYURIDYLIC (POLY AU) INFUSION IN CANCER PATIENTS (MEETING ABSTRACT).

Lenzhofer R, Uchida A, Egger IP, Graninger W

Department of Chemotherapy, University Vienna, Vienna, Austria

Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Clinical investigations have given evidence that interferon preparations may be of therapeutic usefullness in cancer patients. As interferon is available only in small amounts at present, interferon inducing agents seem to be of great importance. A breast cancer study, recently published by Lacour, has demonstrated a significant prolongation of relapse free interval giving Poly AU as adjuvant therapy. We investigated Poly AU (Boehringer Mannheim) for possible interferon induction and immune modulation in cancer patients Poly AU was applied as a single dose of 10 or 150 mg iv. Interferon blood levels were monitored before, 2,4,8,12 and 24 hr after Poly AU application. In no case significant levels of interferon could be detected at the respective intervals. Furthermore Natural killer (NK) cell activity (4h -51Cr-release assay-K 562 target cells) was found unchanged in all patients when investigated before, 2,4,8,12 and 24 hr after Poly AU application. Poly AU added in vitro to human lymphocytes did not change NK-cell activity. Beside this we observed depressive effect (dose dependent) of Poly AU on lymphocytes' blastogenic response to mitogens. Our results indicate that Poly AU application does not induce significant changes in interferon serum levels and NK-cell activity of peripheal blood. (no Refs)

51. INTERFERON INDUCTION IN PRIMATES BY STABILIZED POLYRIBOINOSINIC ACID-POLYRIBOCYTIDYLIC ACID: EFFECT OF COMPONENT SIZE.

Levy HB, Riley FL, Lvovsky E, Stephen EE
Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD, 20205
Infect Immun; 34(2):416-421 1981

Two series of interferon-inducing complexes containing polyriboinosinic and polyribocytidylic acids, poly-L-lysine, and carboxymethyl cellulose were prepared. One series contained carboxymethyl cellulose, 27,000-mol-wt poly-L-lysine, and either 4S, 6S, or 9S polyriboinosinic and polyribocytidylic acids. The other series contained carboxymethyl cellulose, 9S polyriboinosinic and polyribocytidylic acids, and poly-L-lysine, whose mol wt ranged from 2,000 to 27,000. The homogeneity of these double-stranded polynucleotide complexes was confirmed by single-step thermal denaturation profiles and by single peaks in sucrose gradient velocity sedimentation. The complexes have a greater resistance to hydrolysis by ribonuclease than does polyriboinosinic-polyribocytidylic acid. The resistance to ribonuclease increased with the increasing size of polynucleotide homopolymers and poly-L-lysine. In monkeys and, to a lesser extent, in mice, serum interferon levels induced by the different complexes were related to the degree of resistance of the complexes to hydrolysis by ribonuclease. In mice, 4S, 6S, and 9S complexes of polyriboinosinic-polyribocytidylic acid, poly-L-lysine, and carboxymethyl cellulose had a higher level of toxicity than did polyriboinosinic-polyribocytidylic acid as measured by 50% lethal dose. The toxicity was parallel to the ribonuclease resistance of the complexes. It was concluded that an increase in the size of the polynucleotides and the polyamino acids in these complexes leads to higher resistance to hydrolysis by ribonuclease and to greater interferon responses in mice and rhesus monkeys. (Author abstract) (8 Refs)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

52. RAPID EFFECTS OF BCG ON T CELL FUNCTION IN CANCER PATIENTS.

Cannon GB, Reid J, Herberman RB, Connor R, Dean JH, Jerrells T, Perlin E
Dept. Immunology, Litton Bionetics, Incorporated, 5516 Nicholson Lane, Kensington, MD, 20795
Cancer Immunol Immunother; 11(4):265-276 1981

The short-term effects of a single sc injection of BCG on T cell function in cancer patients were studied. Serial blood samples were taken from 48 patients with various cancers and 10 healthy controls. Some patients received 2 x 10(7) or 1 x 10(8) BCG organisms by gun injection. T cell response in all subjects was measured by formation of rosettes with sheep RBC (ERF) and by lymphoproliferative (LP) response to phytohemagglutinin (PHA), purified protein derivative (PPD), and allogeneic cells in mixed lymphocyte cultures. BCG produced a transient increase in ERF and LP response to PPD 3 days after injection. Patients with initially low response to PHA showed an increase on days 3 and 7, while those with initially normal response showed a decrease in response on days 3 and 7. No changes were noted in normal individuals or patients receiving saline or no injections. Apparently BCG has measurable but varied effects on T cell function in some patients. (17 Refs)

53. SUPPRESSION OF IMMUNOLOGICAL RESPONSIVENESS BY IMMUNIZATION WITH BACILLUS CALMETTE-GUERIN CELL WALLS (BCGCW): IN VITRO STUDIES (MEETING ABSTRACT).

Druker BJ, Wepsic HT, Alaimo J, Murray W
Department of Medicine, Barnes Hospitals, St. Louis, MO
Oncodev Biol Med; AbstractsBook,1:37 1981

In vitro experiments were undertaken to determine why systemic immunization with BCGcw caused consistent enhancement of tumor growth of Morris hepatoma tumors in Buffalo or ACI rats. BCGcw immunization stimulated a population of suppressor cells in both the bone marrow and in the spleen and there was an associated decrease in the in vitro blastogenesis response of these cell populations. The in vitro studies are summarized as follows: 1) Normal animals had suppressor cells in their bone marrow but not in their spleen. 2) BCGcw immunized animals showed an increase in suppressive activity in the bone marrow as early as one day after immunization and maximal suppressor activity in the spleen 7-10 days after immunization. 3) Spleen cells from BCGcw immunized rats had decreased reactivity to concanavalin A (con-A) and in the mixed lymphocyte reactivity (MLR) assay. 4) Removal of adherent cells by plastic, nylon wool or carbonyl iron restored the Con-A and MLR reactivity of BCGcw spleen cell populations. 5) The Con-A and MLR reactivities of normal spleen cells could be suppressed by the addition of the BCGcw spleen adherent cell population. 6) Irradiated whole spleen suppressor cells still caused suppression of the Con-A response. 7) The adherent suppressor cells from BCGcw immunized rats suppressed Con-A reactivity across a major histocompatible barrier. (no Refs)

54. THE BINDING OF BCG-ACTIVATED MACROPHAGES TO TUMOR TARGETS STIMULATES SECRETION OF CYTOLYTIC FACTOR.

Johnson WJ, Whisnant CC, Adams DO
Dept. Pathology, Duke Univ. Medical Center, Durham, NC, 27710
J Immunol; 127(5):1787-1792 1981

The binding of neoplastic targets and the secretion of a potent cytolytic protease (CF) by BCG-activated macrophages have previously been shown to be independent functions, both of which are necessary for completion of macrophage-mediated cytolysis. The present studies demonstrate that secretion of CF is triggered by the binding of neoplastic targets to BCG-activated macrophages. The binding of tumor targets, but not of normal lymphocytes, resulted in enhanced secretion of CF from BCG-activated macrophages, although not from macrophages elicited by thioglycolate broth. Dead or metabolically inactive tumor targets, as well as membrane preparations of tumor targets, induced secretion of CF from BCG-activated macrophages. The blocking of macrophage-target binding with a porous filter prevented augmented secretion of CF. Appreciable secretion of CF occurred in as little as 30 min after addition of tumor targets to BCG macrophages. Binding did not induce a generalized increase in secretion of neutral proteases by BCG macrophages, since secretion of plasminogen activator was actually decreased after the binding of P815 targets. The data suggest the selective binding of BCG-activated murine macrophages to neoplastic targets triggers the secretion of a potent CF. (Author abstract) (33 Refs)

55. EVIDENCE FOR TWO DISTINCT POPULATIONS OF SUPPRESSOR CELLS IN THE SPLEENS OF MYCOBACTERIUM BOVIS BCG-SENSITIZED MICE.

Turcotte R
Centre de Recherche en Bacteriologie, Institut Armand-Frappier, Universite de Quebec, Ville de Laval, Quebec H7V 1B7, Canada
Infect Immun; 34(2):315-322 1981

Spleen cells from female C57BL/6 mice infected iv with 1 mg (about 10(7) viable units) of BCG were shown to suppress the blastogenic responses induced by the T-cell mitogens phytohemagglutinin and concanavalin A and by the B-cell mitogen lipopolysaccharide in spleen cells from normal syngeneic mice. By using various separation procedures or cellular treatments, evidence was found for two distinct populations of splenic suppressor cells. One population belonged to the monocyte-macrophage lineage on the basis of their adherence to plastic surfaces, their removal after treatment with carbonyl iron, and their resistance to gamma irradiation. The other population of suppressor cells belonged to the T lymphocytes due to their sensitivity to an anti-Thy 1 antiserum and complement and to gamma irradiation. After separation on nylon wool columns, inhibitory activity was found in both the nonadherent and the adherent spleen cell populations. Both populations of suppressor cells were present in the spleens 14 days after BCG inoculation and persisted for at least 40 days after infection. (Author abstract) (20 Refs)

56. CHEMOIMMUNOTHERAPY OF MURINE BLADDER CANCER.

Stogdill BJ, Lamm DL, Livingston RB
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Invest Urol; 19(3):179-181 1981

The lethality of invasive transitional cell carcinoma (TCC) has prompted a search for effective, minimally toxic, adjuvant therapy. Such agents were evaluated in a murine bladder cancer (MBT2) model which parallels the clinical disease. One hundred C3H/He mice were inoculated id with 2.5 x 10(4) viable MBT2 tumor cells and randomized to receive either normal saline (control), cis-Platinum, cyclophosphamide (CY), methotrexate (MTX), BCG, (CY + MTX), or (CY + MTX + BCG). Chemotherapy was given ip weekly starting on Day 7 after inoculation. Immunotherapy was given intralesionally on days 1 and 10 only. All mice were treated for 5 wk followed by 5 wk of observation. A 5 wk, tumors of mice receiving CY alone or either of the combinations of therapy were smaller (p less than 0.01) than tumors of controls or other single agents alone. Each regimen increased survival, but only the combination regimen increased survival significantly (p less than 0.01). In the doses and schedule used in this model, combination chemotherapy and chemoimmunotherapy significantly delay tumor growth and increase duration of survival (p less than 0.01) when compared with controls or single agent groups. (Author abstract) (7 Refs)

57. CORYNEBACTERIUM PARVUM STIMULATION OF ADHERENT AND NON-ADHERENT CYTOTOXIC CELLS IN MICE.

Hassan ZM, Rees RC, Potter CW
Dept. Virology, Academic Div. Pathology, Univ. Sheffield Medical Sch., Sheffield S10 2RX, England
Br J Cancer; 44(4):532-538 1981

Two naturally occurring cytotoxic cell populations have been identified in the peritoneal cavity of mice inoculated with C parvum (CP), and are distinguishable on the basis of target-cell reactivity and intrinsic properties. The first effector cell was non-adherent to nylon wool and glass and non-phagocytic. These cells were selectively cytotoxic to the NK-sensitive target cell line K562, and present in the peritoneal cavity of mice 2 days after treatment with 700 ug of CP. The second cytotoxic effector cell was adherent to nylon wool and glass, and killed EL4 lymphoma cells derived from in vivo tumor transplants; these target cells are susceptible to phagocytic cell killing, but not NK-cell cytotoxicity in short-term (4h) assays. The adherent cytotoxic population of effector cells was present 4 days after inoculation of CP. In vivo studies showed that CP injected ip induced resistance to ip challenge with lymphoma EL4 cells, but no resistance was evident when the challenge dose was administered sc. Adoptive-transfer studies showed that the effector cell type responsible for inhibiting tumor growth was nylon-wool adherent, probably CP-activated macrophages. (Author abstract) (26 Refs)

58. SUPERIORITY OF MICROCOCCUS LYSODEIKTICUS TO BCG IN CHEMO-IMMUNOTHERAPY OF ADVANCED L1210 LEUKAEMIA.

Verloes R, Atassi G
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Eur J Cancer Clin Oncol; 17(8):849-956 1981

When CDF1 mice initially inoculated with 10(5) leukemic cells were treated once by 12 mg/kg of nitroso-urea BCNU (carmustine)on day 6.5 (when the tumor burden reaches greater than 10(8) cells) and by 1 mg Micrococcus injections by days 8, 11, 14, 17 and 20 or on days 8, 9, 10, 11 and 12, 30% of cured mice were recorded. Immunotherapy with 1 mg injections of BCG, B subtilis or Micrococcus lysodeikticus given on days 8, 11, 14, 17 and 20 after BCNU chemotherapy (1 12 mg/kg injection on day 6.5) respectively cured 5, 10 and 50% of leukemic mice after a graft of 4,000 L1210 cells on day 0 and 0, 10 and 50% of leukemic mice after a graft of 25,000 cells. Using this chemo-immunotherapy combination, Micrococcus immunotherapy proved to be significantly effective (X2 test, p less than 0.005) against greater than 10(8) L1210 cells whereas B subtilis or BCG immunotherapy was not statistically significant. Mice cured by chemo-immunotherapy (BCNU + Micrococcus) rejected new local as well as systemic grafts of 10(4) L1210 cells (on day 120). (Author abstract) (35 Refs)

59. TREATMENT OF FELINE LYMPHOSARCOMA AND FELINE LEUKEMIA VIRUS (FELV) BY EX VIVO IMMUNOSORPTION USING STAPH. AUREUS COWAN I: EFFECTS ON CIRCULATING IMMUNE COMPLEXES, COMPLEMENT, AND TUMOR ANTIBODY (MEETING ABSTRACT).

Jones FR, Yoshida LH, Hardy WD, Good RA, Day NK
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. The Association 187 pp., 1981.

FeLV is the etiologic agent of cat lymphosarcoma (LSA). Spontaneously occurring FeLV-IFA positive, LSA or FeLV-IFA positive, tumor-free pet cats were treated by low-dose, whole-body irradiation and ex vivo immunosorption using Staphylococcus aureus Cowan. Cats responded by reduction of tumor and in several cases, a complete and long-lasting (one yr or more) regression. Most importantly, there were cases of FeLV-IFA positive cats that changed to a FeLV-IFA negative status. In vitro studies of the cat's sera indicate a decrease of circulating immune complexes detected by Raji cell radioimmunoassay from pre-treatment to post-treatment (eg 1128 to 288; 792 to 24; 2320 to 200; 368 to 240 ug equivalent cat aggregated gammaglobulin/ml respectively; normal value 85 +/-65 ug/ml). There was a commensurate increase in the level of total hemolytic complement (18 to 50; 17 to 25; 8 to 60; 59 to 90 CH50 units/ml respectively; normal value 92 +/-27). There was an increase in antibody to the cat LSA tumor-specific antigen Feline Oncornavirus cell membrane antigen (FOCMA) from undetectable prior to treatment to titers less than or equal to 1:4 after treatment which corresponded to LSA regression and reversal of FeLV infection. These data suggest an immune response of the host as part of the mechanism for tumor regression and anti-viral response. The effects of irradiation alone and immunosorption alone are presently being investigated. (1 Ref)

60. EXTRACORPORAL PLASMA ABSORPTION WITH COWAN I STAPHYLOCOCCI IN MALIGNANT DISEASE (MEETING ABSTRACT).

Persson B, Braide I, Falsen E, Lindholm L, Rudenstam CM
Sahlgren Hospital, University of Goteborg, Goteborg, Sweden
W.H.O. Seminar on Malignant Melanoma, June 24, 1981, Gothenburg, Sweden. World Health Organization 35 pp., 1981.

Plasma from patients with malignant disease has been absorbed in vitro with formalin and heatkilled Cowan I staphylococci and the treated plasma has been retransfused. Two to three liters of plasma were routinely treated using a total of 40-60 g of staphylococci. Most of the patients were treated on several occasions. Nine patients were treated: 6 malignant melanomas, 1 pancreatic cancer, 1 colon carcinoma and 1 hypernephroma. All patients were disseminated and most of them in a bad general condition. All patients reacted with fever and chills when the treated plasma was retransfused. Two patients developed severe respiratory distress and one patient developed a hemorrhagic diatesis in the whole gastrointestinal-tract. Further, some of the patients reacted with severe pain over the tumor site. In 5 of the patients we had a positive effect of the plasmapheresis with an improvement in general condition and decrease in tumor size as determined by computer tomography, histopathological examination or ultrasound. Positive effects of the treatment did not correlate to the presence of immunocomplexes before treatment or to any of the in vitro parameters studied. (no Refs)

MICROBIAL FRACTIONS AND EXTRACTS

61. SUPPRESSION OF IMMUNOLOGICAL RESPONSIVENESS BY IMMUNIZATION WITH BACILLUS CALMETTE-GUERIN CELL WALLS (BCGCW): IN VIVO STUDIES (MEETING ABSTRACT).

Wepsic HT, Druker BJ, Alaimo J, Murray W, Vranes A
Department of Pathology, Loyola University School of Medicine, Maywood, IL
Oncodev Biol Med; AbstractsBook,1:37 1981

In vivo experiments were undertaken to determine why systemic immunization with BCGcw caused consistent enhancement of tumor growth of Morris hepatoma tumors in Buffalo or ACI rats. BCGcw immunization stimulated a population of suppressor cells that blocked the inductive phase of both tumor specific immune responses as well as allograft immune responses. BCGcw immunization therefore induced a state of immunological unresponsiveness. When 6x10(6) 3924a ascites tumor cells were inoculated id into ACI rats, tumor did not grow and tumor specific immunity was stimulated. Immunization with BCGcw not only blocked the induction of this tumor immunity but it caused the progressive growth of syngeneic tumors at the id tumor site. Previously established syngeneic tumor immunity was not affected. When an ACI tumor (3924a) was inoculated id, into Buffalo rats no tumor growth occurred. Immunization with BCGcw caused the transient, and on occasion, the progressive growth of the ACI tumor allograft 3924a in Buffalo rats. When lethally irradiated ACI rats were repopulated with normal spleen and/or bone marrow from Buffalo rats fatal graft vs host disease occurred. Repopulation of lethally irradiated ACI rats with spleen and/or bone marrow from Buffalo rats, which were immunized with BCGcw, resulted in a decrease in the graft vs host disease and an increase in the overall survival of rats. (no Refs)

62. IN VITRO AND IN VIVO ACTIVATION OF HUMAN LYMPHOCYTE CYTOTOXICITY IN MELANOMA PATIENTS BY OK-432 (MEETING ABSTRACT).

Kokoschka EM, Micksche M, Uchida A, Knobler R
IInd Department of Dermatology and Institute for Cancer Research, University of Vienna, Vienna, Austria
Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

OK-432, a streptococcal preparation, has been used with increased frequency as an immunotherapeutic agent in the therapy of human cancer in Japan. The follow up of OK-432 therapy schedules has shown that several immune parameters appear improved. The present study was designed to investigate clinical relevance and the effect on lymphocyte cytotoxicity of OK-432 on melanoma patients in continuation of a phase I study. A single dose of OK-432 significantly enhanced natural killer (NK) activity of 562 target cells, determined in a 4 hr chromium release assay. The cytotoxic reaction was induced by application of OK-432, ic, im and iv. The max of the reaction was observed 72 hr after application, NK activity of blood lymphocytes of melanoma patients and normal donors was significantly enhanced by in vitro treatment with OK-432 (0.5 KE ml, 20 hr). Lymphocytes from pleural effusion of melanoma patients exhibiting no NK activity were also activated by OK-432. Human type I interferon had a comparable effect on NK cells. OK-432 was able to activate both NK-enriched and depleted reactions suggesting that the substance may not only augment cytotoxic activity of preexisting NK cells but also generate new cytotoxic cells. The latter cells were found to mediate cytotoxicity against autologous fresh tumor cells. These in vitro investigations exhibit good correlation with our clinical results with OK-432 in melanoma patients. (1 Ref)

63. EXPERIMENTAL AND CLINICAL INVESTIGATIONS WITH OK-432-A STREPTOCOCCAL PREPARATION WITH IMMUNE MODULATING PROPERTIES (MEETING ABSTRACT).

Micksche M, Kokoschka EM, Uchida A
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Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

OK-432-a non viable Streptococcus preparation - is now intensively investigated in Japan for immune modulation in cancer patients. We have performed experimental and clinical investigations to obtain information on the activity spectrum of OK-432. First we found that doses of 100KE/mg of OK-432 significantly enhances natural killer (NK)-cell activity of mouse splenocytes (max 36 hr after iv). In Lewis lung tumor system we have demonstrated that OK-432 therapy (100 KE/kg x 7 iv route) reduces a significant number of lung metastases. Furthermore we demonstrated a significant enhancement of cytotoxic activity of cancer patients' peripheral blood and pleural effusion-derived mononuclear cells upon in vitro incubation with OK-432. The effect was time- and dose-dependent and comparable with that of interferon (HIFN), although OK-432 seems to enhance cytotoxicity of adherent and nonadherent effector cells. In a phase I clinical trial we have demonstrated an immune modulation by OK-432 (restoration of delayed cutaneous hypersensitivity reactions, lymphocyte blastogenic response and NK-cell activity) due to a reduction of suppressor cell activity. Besides these effects on immune functions we also observed some clinical benefit for treated cancer patients. OK-432 seems to be a potent immune modulating agent which should be further investigated for clinical efficacy. (no Refs)

64. YEAST CELLS AND GLUCAN GHOSTS AS IMMUNOPOTENTIATORS OF ANTI-CANCER CHEMOTHERAPY IN MOUSE LEUKEMIA MODELS (MEETING ABSTRACT).

Cassone A, Marconi P, Bistoni F, Mattia E, Cenci E, Pesce CD, Tissi L

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Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Merthiolate- or glutaraldehyde-inactivated yeast cells of Candida, Saccharomyces and Cryptococcus spp strongly potentiate the effects of chemotherapy in murine tumor models. In a typical experiment, CD2F1 mice were inoculated ip with 10(6) histocompatible LSTRA cells and treated 5 days after with bis,1-chloroethyl nitrosourea (BCNU; 18mg/kg): significant increase of antitumor efficiency of BCNU treatment was afforded by giving 2x10(7) cells of Candida albicans (CA) ip both before and after tumor challenge. Following CA administration on days-14, +1, +8, there was 100% survival at the 60th day as compared to median survival x (MST) of 8 and 17 days of untreated and BCNU-treated mice respectively. CD2F1 mice challenged with 10(6) histocompatible L1210 leukemia cells and treated with CA and BCNU according to the scheduling above, gave MST values comparable to those shown for the LSTRA model. The potentiation of BCNU-chemotherapy by CA was of immunoadjuvant (IA) type and, like that of other classic IAs such as BCG or Corynebacterium parvum was abolished by total body irradiation (400 R) of mice 5-6 hr before the first IA administration. Soluble mannan or glucan-protein fractions extracted from yeast cell wall were devoid of any IA effect nor were they capable of boosting the first treatment with whole CA cells. Only the alkali-acid insoluble wall ghosts made up of fibrous 1,3-1,6 glucan plus minute amounts of chitin, did manifest and effect comparable to that of whole yeast cells. However, glucan ghosts showed a high anti-tumor activity when injected ip on day-14 or-7 only, without boosting on day +1, suggesting that differences exist in the immunological mechanisms by which whole cells and glucan ghosts potentiate BCNU chemotherapy in these experimental models. (no Refs)

65. POTENTIATED IMMUNE RESPONSES AFTER ADMINISTRATION OF ACLACINOMYCIN (MEETING ABSTRACT).

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Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

After ip injection of aclacinomycin into mice, a variety of immune responses were increased. The total plaque forming spleen cell response to sheep RBC was higher in treated animals than in controls, in spite of an apparent cytotoxic effect on B-cells. Similarly, the graft-versus host reactivity of spleen cells and purified spleen T-cells was augmented in treated animals. Such effects might arise from the inactivation of a suppressor cell population; and the aclacinomycin-sensitive cells is apparently a long-lived cell, surviving adult thymectomy. Delayed-type hypersensitivity reactions were also augmented in treated animals, particularly those bearing tumors. In adjuvant treated mice (BCG or Azimexon), the injection of aclacinomycin augments the immune response still further. Such observations should be taken into account in the establishment of clinical protocols associating immunotherapy and chemotherapy. (no Refs)

66. PASSIVE PROTECTION AGAINST X-IRRADIATION WITH SERUM FROM ZYMOSAN-PRIMED AND ENDOTOXIN-INJECTED MICE.

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J Reticuloendothel Soc; 30(4):301-311 1981

Pretreatment with small amounts of bacterial lipopolysaccharide (LPS) is known to protect conventional mice against lethal x-irradiation for a period of at least 28 days, but neither tolerant nor nonresponder C3H/HeJ mice can be protected. Zymosan and other activators of the reticuloendothelial system also protect conventional mice. These observations have been confirmed and extended in this report and show in addition that serum from Zymosan A-pretreated mice collected 2 hr after a small dose of LPS can be used to protect tolerant and C3H/HeJ mice against x-irradiation. Sera from conventional mice collected similarly after an injection of either 10 or 50 ug LPS were not radioprotective. All three sera were active to a comparable degree in stimulating in vitro colony formation by bone marrow cells derived from either CF-1 or C3H/HeJ mice. The protective serum, when divided into three pools following sieve chromatography with Ultrogel AcA 34, was fully protective when the high mol wt components were preinjected while the fraction with the smallest molecules gave partial protection. The fraction with intermediate-sized protein was inactive. Each of the three fractions of serum that was passively protective was tested for colony-stimulating activity (CSA). Much of the CSA of the original serum was lost and most of the 40% that remained was in the protective fraction. It is apparent from these results that protection of mice against x-ray death with serum mediators elicited by an injection of LPS is not dependent upon CSA levels alone. (Author abstract) (30 Refs)

CYTOKINE THERAPY

67. TUMOUR-NECROSIS FACTOR FROM THE RABBIT. V. SYNTHESIS IN VITRO BY MONONUCLEAR PHAGOCYTES FROM VARIOUS TISSUES OF NORMAL AND BCG-INJECTED RABBITS.

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Br J Cancer; 44(3):418-424 1981

Tumor-necrosis factor (TNF) is an anti-tumor factor released into the serum of BCG-primed rabbits after iv injection of endotoxin. Although negligible amounts of TNF are produced in normal, unprimed animals after endotoxin injection, monocytes from these rabbits can produce TNF after endotoxin challenge in vitro. This paper (a) establishes the optimal conditions for TNF production in vitro by mononuclear phagocytes from various tissues and (b) compares tissues from normal and BCG-injected rabbits for TNF production in vitro. Optimal amounts of TNF are produced by mononuclear phagocytes in the presence of endotoxin. The TNF is newly synthesized, mainly in the first 7 hr of culture, and has similar gel-filtration and ion exchange behavior irrespective of its source. For both normal and BCG-injected rabbits, alveolar and peritoneal macrophages are the most potent producers, followed by blood monocytes, spleen macrophages and marrow cells. The liver is also an important site of TNF synthesis. In the tissues of BCG-injected rabbits there are more mononuclear phagocytes than in normal rabbits, and these cells have enhanced capacity to product TNF. Taking both factors into account it can be calculated that, after injection of endotoxin in vivo, over 20 x more TNF would be produced by BCG rabbits than normal rabbits, assuming that the major sources of production are the lungs, blood, spleen and liver. (Author abstract) (8 Refs)

68. BIOLOGIC PROPERTIES OF CHROMATOGRAPHICALLY SEPARATED MURINE THYMOMA-DERIVED INTERLEUKIN 2 AND COLONY-STIMULATING FACTOR.

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J Immunol; 127(5):1983-1987 1981

Two growth factors, Interleukin 2 (T cell growth factor) and colony-stimulating factor, are produced concomitantly by a murine EL-4 thymoma cell line after stimulation by phorbol myristate acetate. As shown elsewhere, these thymoma-derived factors appear to be biochemically and functionally indistinguishable from the Interleukin 2 and colony-stimulating factor produced by mitogen-stimulated mouse spleen cells. Both factors co-elute during gel filtration with apparent mol wt in the range of 30,000, and both exhibit overlapping isoelectric point profiles between pH 4 and pH 5. Because we were unable to separate these two factors by methods based on either mol wt or charge, we have used phenyl-Sepharose chromatography, a method based on hydrophobic interactions, to completely separate murine Interleukin 2 and colony-stimulating factor. In contrast with published reports, each of the separated factors exhibits unique biologic activities on lymphocytes and macrophages. Interleukin 2 provides help for antibody synthesis in the nude mouse, but neither enhances interferon production by macrophages nor stimulates macrophage growth. Colony-stimulating factor does not enhance antibody synthesis in the nude mouse but does enhance interferon production by macrophages and stimulate macrophage growth. (Author abstract) (29 Refs)

THYMIC HORMONES AND OTHER IMMUNORESTORATIVE AGENTS

69. MANIFESTATION AND GROWTH OF TRANSPLANTABLE OSTEOSARCOMA IN MICE: THE EFFECT OF THYMECTOMY AND THYMOSIN TREATMENT.

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Clin Orthop; (159):279-285 1981

The effect of thymectomy and thymosin (TS) treatment on tumor growth, structural appearance and immunity was studied in male CBA mice inoculated with tumor cell suspensions originating from the Dunn osteosarcoma. The mice were divided into five groups (Group I controls, Groups II and IV thymectomized, and Groups III and IV TS-treated) with 15-17 mice/group. In Groups I, III, and IV, the tumor frequency was 80-94%, while in Group II, a significantly higher proportion (p less than 0.001) of mice were tumor free (tumor frequency 47%). Group II also showed the lowest mean tumor wt. No obvious structural differences were found among the tumors of the different groups. However lymphocytic infiltration with a slight admixture of plasma cells was observed at the periphery of Group II tumors. In all groups, very low specific lysis was observed; only at a lymphocyte/tumor cell ratio of 300:1 was a significant difference established. Group II mice showed a higher degree of cytotoxic activity (p less than 0.01) than the rest of the groups. Normal animals not subject to tumor cell injections responded in the same apparent magnitude as Groups I, III, and IV. Even extensive immunization produced no measurable increase in lysis. Neither cytotoxic nor growth inhibiting antibodies were found in any of the sera tested. No significant correlation was seen between tumor wt and specific lysis of tumor cells, although the five animals with the highest specific lysis were tumor-free. The results indicated that CBA mice bearing this osteosarcoma did not develop cell-mediated or humoral-immune response against the tumor. (15 Refs)

70. ANTI-TUMORAL EFFECT OF IN VITRO THYMOSIN PREINCUBATED SYNGENEIC BONE MARROW CELLS IN MICE (MEETING ABSTRACT).

Cupissol D, Goldstein AL, Serrou B
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Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

We have previously shown that syngeneic bone marrow cells (a system directly applicable to that employed for cancer patients for autologous bone marrow transplantation, did not enhance tumor growth in mice. Following in vitro Thymosin pre-incubation, syngeneic bone marrrow cells significantly prolonged the survival time. In the present study, we were able to show that 1) this phenomenon is T lymphocyte dependent and disappeared when the bone marrow cells were treated with an anti-Thy 1-2 anti-serum. 2) This phenomenon is not dependent on natural killer activity; treatment of mice by radioactive strontium does not change the anti-tumoral effect. 3) Thymosin seems to act on helper T cells and not in the suppressor T cells. The antitumoral effect disappears when the bone marrow cells are treated by an anti Ly T1 antiserum but persists when the bone marrow cells are treated by an anti Ly T-2-3 antiserum. These results are sufficiently encouraging to support a randomized study in patients bearing advanced solid tumors using autologous bone marrow cell (preincubated or not with Thymosin) transplantation after high dose chemotherapy. (no Refs)

71. DEFINITION OF THE ACTIVITY OF PEPTIDES ISOLATED FROM THE THYMIC EXTRACT TP-1 (THYMOSTIMULIN) (MEETING ABSTRACT).

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Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

A thymic extract, TP-1 (Thymostimulin), was shown to have antiviral and antitumoral activities, conceivably mediated by modulation of host defense mechanisms, beside a restorative effect of cellular immunodeficiency. The activity of several peptides isolated from TP-1 was analyzed in vitro, using mouse and human lymphocytes. One of the peptides strongly induced the differentiation of mouse T cells from prothymocytes to Thy-1 positive cells but did not induce B cell differentiation - suggesting a thymic specific activity. The same peptide had a similar effect on T but not on B lymphocytes of human cord blood. In addition, this peptide strongly modulated lymphocyte proliferative response to tumor cells and plant lectins, lymphocytotoxicity induced in vitro, regulatory cell activity and interferon production. This peptide is immunochemically and electrophoretically different from thymopoietin. A second peptide had immunochemical, electrophoretic and biological characteristics of ubiquitin, a non-specific ubiquitous cell component. It induced the acquisition of both T and B cell differentiation markers and had also some effect on lymphocyte function. A third peptide was devoid of activity on surface markers, but had a selective and uniquely high activity on stimulation of lymphocytes by low doses of phytohemagglutinin. Studies are underway to find out whether antiviral and antitumoral activities of TP-1 represent a composite effect of its several components or only one of them is the active ingredient. (1 Ref)

72. EFFECT OF THYMUSTIMULIN (TP-1) ON MOUSE RESPONSES AGAINST LYMPHOMA CELLS (MEETING ABSTRACT).

Menconi E, Barzi A, Nardelli B, Giampietri A
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Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Thymustimulin (TP-1, Serono) is a calf thymic extract which proved, in immature T-cells, to be able of inducing several properties of mature T-cells, such as the appearance of specific markers and increased effector and proliferative functions. Previous findings from our laboratory showed that the in vitro generation of murine alloreactive T-lymphocytes, impaired by gamma rays or cyclophosphamide (Cy), could be restored by in vitro preincubation of responder cells with TP-1. In the present study we explored the effects of in vivo treatment with TP-1 on some T-dependent functions such as: a) the in vivo antilymphoma allograft response to L1210 leukemia by H-2-incompatible C3H mice pretreated with Cy (200 mg/kg) 7 days before the ip tumor challenge with 10(6) cells. The results, expressed as median survival time, show that exposure of mice to TP-1 (0.4, 1.4 or 2 mg/kg ip or 1.4 mg/kg iv on days 1, 3, 5 after Cy administration) is able to partially reverse the immunodepressive effect of Cy; b) the in vitro secondary cell-mediated cytotoxicity to compatible virus-induced LSTRA lymphoma using lymphocytes from (BALB/c x DBA/2) Fl (CD2F1) mice inoculated with Cy (180 mg/kg) at the time of the primary in vivo immunization. The mice were injected ip with TP-1 (2 and 4 mg/kg) for 10 consecutive days before spleen collection for the secondary in vitro 5-days culture. 51Cr-release assay was performed against LSTRA target. The results showed that TP-1 can restore the ability of Cy-exposed splenocytes to mount the secondary cytotoxic response to virus-mediated antigens associated with LSTRA. The present results confirms our previous findings that TP-1 is capable of reversing the Cy-induced impairment of cell-mediated responses, possibly through increased T-cell differentiation. (no Refs)

73. INFLUENCE OF SERUM THYMIC FACTOR (F.T.S.) ON RADIATION-INDUCED LEUKAEMOGENESIS IN THYMECTOMIZED AKR MICE (MEETING ABSTRACT).

Legrand E, Daculsi R, Bach JF, Duplan JF

No affiliation given

Exp Hematol; 9(Suppl9):67 1981

The influence of serum thymic factor (FTS) on extra-thymic leukemogenesis induced in thymectomized AKR mice fractionated sub-lethal irradiation was studied. Thirty day-old thymectomized mice were submitted to 4 weekly doses (1.75 Gray) and thereafter treated with FTS (1 ng) for 9 days. Two groups were restored with either bone marrow (BM) or spleen cells prior to FTS treatment. In another group, mice were treated with FTS (12 ng) for one mo after thymectomy and prior to irradiation. Results indicated that primarily irradiation and FTS, and to lesser extents, restoration and age of the mice at the time of their first radiation exposure influenced leukemogenesis. Irradiation increased the spontaneous low incidence of extra-thymic leukemia up to 50%. Although indication about the expression of endogenous retroviruses in thymectomized AKR is still missing, the possible expression of leukemogenic recombinants either identical to or different from AKR MCF viruses might explain the enhancing effect of radiation in leukemogenesis. Mice developed two types of leukemias: 'null' leukemias whose cells did not bear any detectable theta antigen or surface immunoglobulin and B leukemias. Among the null leukemias, two kinds could be distinguished: 'early' ones which were observed before 450 days, and in which BM and spleen were similarly involved; 'late' ones which displayed the same characteristics as B leukemias ie delayed appearance and splenic origin. Although FTS did not modify the overall frequency of leukemias, it increased significantly the incidence of the 'early' null ones. It had no effect on the frequency nor the latency of late null and B leukemias. Any population of theta negative T cells sensitive to FTS could be an acceptable candidate for 'early' null leukemogenesis. (no Refs)

ACTIVE SPECIFIC IMMUNIZATION

74. IMMUNOPREVENTION OF TYPE-C VIRUS-INDUCED MURINE LEUKEMIAS BY VACCINATION WITH VIRAL ENVELOPE POLYPEPTIDES (MEETING ABSTRACT).

Hunsmann G, Schneider J
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. The Association 187 pp., 1981.

Prevention of virus-induced murine leukemia was attempted by active immunization with subunit vaccines in two different models: erythroleukemia developing in STU mice after experimental injection of Friend virus complex and spontaneous thymic leukemia of AKR mice. Highly purified envelope polypeptides prepared from Friend (FLV)-, AKR- and feline (FeLV) leukemia virus were emulsified in incomplete Freund's adjuvant and used as immunogens. First results showed that 20/20 STU mice immunized with 100 ug of FLV gp85 survived a challenge dose of FLV inducing fatal erythroleukemia in 90-100% of unvaccinated controls, while 3/7 animals receiving 10 ug of FLV gp85 died with leukemia. Smaller doses were either ineffective, as was adjuvant alone, or even shortened the survival time. Immunization with 100 ug of FLV gp71 was inferior to the same dose of gp85, (2/6 mice died after challenge) but was superior to isolated p15E. Only the immune response to glycoprotein 71 seems to reduce mortality and is probably developed more strongly when gp85 is used as immunogen. The internal core protein p30 and adjuvant alone were ineffective as vaccines. (no Refs)

75. IMMUNOTHERAPY WITH IRRADIATED TUMOUR CELLS AND BCG IN EXPERIMENTAL OSTEOSARCOMA.

Larsson SE, Lorentzon R, Boquist L
Dept. Orthopaedic Surgery, Univ. Umea, Umea, Sweden
Acta Orthop Scand; 52(5):469-473 1981

Effects of immunotherapy with irradiated tumor cells and BCG were studied in a non-metastasizing variety of Dunn osteosarcoma transplantable in CBA mice. A group of experimental mice preimmunized by sc injections of 1.4, 1.4 and 0.7 x 10(6) irradiated tumor cells/animal 3, 2, and 1 wk before sc administration of 1.0 x 10(6) liver tumor cells/animal showed a tumor incidence of 23%, which was significantly (p less than 0.005) lower than the 92% incidence in control mice. Freeze-dried Danish BCG vaccine, injected sc in mice at a dose of 1.0 mg of dry wt in 0.2 ml of Sauton soln, was repeated twice at 3-wk intervals. Fou rteen days after the last injection, 1.3 x 10(6) living tumor cells/animals was administered sc. Tumor incidence in BCG-treated mice was 90%, compared to 94% in controls that received only Sauton soln. No structural differences were seen between the various groups by light and electron microscopy. Alkaline phosphatase activity was exhibited histochemically in all tumors. (13 Refs)

76. EFFECT OF ANTINEOPLASTIC AGENTS ON THE INDUCTION OF SUPPRESSOR MACROPHAGES BY CONCANAVALIN A-BOUND TUMOR VACCINE.

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Cancer Res; 41(12):5151-5157 1961

The present study was undertaken to identify tumor vaccine-induced suppressor cells and to examine the effect of antineoplastic agents on their production and suppressor activity. Primary and secondary sensitization with concanavalin A (con A)-bound L1210 murine leukemia cell vaccine induced suppressor cells in the peritoneal cavity of histocompatible BALB/c x DBA/2Cr F1 mice. These cells phagocytized latex beads and adhered to plastic vessels. Their suppressor cell activity, determined by polyclonal in vitro spleen cell blastogenesis, was abrogated by silica but not by rabbit anti-mouse brain antiserum and complement. This evidence led to the conclusion that the suppressor cells were macrophages. The production of suppressor macrophages depended on both the Con A-free vaccine cells and vaccine-bound Con A molecules since, singly, neither induced the corresponding suppressor cell activity. Although the induced suppressor cells were not abrogated by mitomycin C in vitro and cyclophosphamide in vivo, the increase of peritoneal suppressor cells following the second vaccination and/or their suppressor activity was significantly inhibited by antineoplastic agents including cyclophosphamide, mitomycin C, and 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2 chloroethyl)-1-nitrosourea hydrochloride. The finding that vinblastine preferentially inhibited the increase of peritoneal suppressor cells suggested that these agents interfered with the proliferation of suppressor cells (and/or their progenitor cells) in response to the second vaccination. The close correlation between the potency of these antineoplastic agents in inhibiting the production of suppressor cells and the induction enhanced antitumor immunity by Con A-bound tumor vaccine supports the feasibility of the proposed combination of chemotherapy and immunotherapy in which antineoplastic agents are dually effective by killing tumor cells and eliminating the vaccine-associated suppressor cells. (Author abstract) (11 Refs)

ADOPTIVE IMMUNIZATION AND RELATED APPROACHES

77. DEFINITIVE EVIDENCE THAT NATURAL KILLER (NK) CELLS INHIBIT EXPERIMENTAL TUMOR METASTASIS IN VIVO.

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J Immunol; 127(5):1754-1758 1981

Effector lymphoid cells that inhibit hematogenous tumor metastases in normal unimmunized mice were studied. Mice pretreated with cyclophosphamide (Cy) exhibited a diminished ability to destroy circulating tumor cells, which, in turn, caused an increased incidence of experimental pulmonary metastasis. Adoptive transfer of spleen cells from unimmunized syngeneic donors abrogated the Cy-induced enhancement of metastasis formation. The effector cell active in these adoptive transfer experiments was sensitive to treatment with specific anti-NK-1.2 antibodies and complement. This treatment was shown by in vitro tests to deplete or inactivate NK cells selectively. These findings provide direct evidence that NK cells play a significant role in the inhibition of hematogenous tumor metastasis in vivo. (Author abstract) (26 Refs)

78. KEYHOLE-LIMPET HAEMACYANIN AND IMMUNE RIBONUCLEIC ACID IMMUNOTHERAPY OF MURINE TRANSITIONAL CELL CARCINOMA.

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Urol Res; 9(5):227-230 1981

The immunotherapeutic potential of keyhole-limpet hemocyanin (KLH) and immune RNA extract was evaluated in C3H mice bearing a transplanted syngeneic transitional cell carcinoma. Mice in groups of 15 animals each received (1) footpad injections of KLH (50 ug) 3 wk prior to transplantation and intralesional injections on days 1 and 7 after transplantation, (2) footpad injections of immune RNA (1 mg) 3 days before transplantation, on the day of transplantation, and on days 2, 4, 6, and 8 after transplantation, or (3) intralesional injections of immune RNA (2.5 mg), tumor antigen, and nonimmune peritoneal exudate cells before and 7 days after transplantation. KLH treatment caused significant reduction in tumor growth and significant prolongation of survival. Neither local nor systemic immune RNA treatment inhibited tumor growth. (20 Refs)

SEROTHERAPY AND RELATED APPROACHES

79. IMMUNOSUPPRESSIVE AND ANTILEUKEMIC EFFECTS OF ANTI-T: EXPERIMENTAL STUDIES (MEETING ABSTRACT).

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Exp Hematol; 9(Suppl9):120 1981

High titer cytotoxic, complement-fixing mono- or polyclonal antibodies against T antigens were applied in order to suppress graft-versus-host (gvh) or host-versus-graft reactions as well as T cell leukemias in mice. While rabbit antilymphocytic serum suppressed host-versus-graft reactions, mono- and polyclonal anti-Th-1 alone or combined with monoclonal antibodies against B lymphocytes had surprisingly little immunosuppressive effect. From this and othe data a defense mechanism is postulated which prevents T cell depletion following injection in mice of cytotoxic antibodies against T epitopes. Thus monoclonal antibodies against presently known epitopes may not fulfill all expectations concerning immunotherapy when injected in vivo. However incubation in vitro of donor marrow with anti-Th-1 suppressed gvh. Without addition of complement an inverse relation between gvh-suppression by anti-T and donor-recipient histoincompatibility is evident particularly what regards gene-dose effects. Suppression with anti-T of T leukemia cells in marrow transferred to syngeneic mice requires the presence of complement and may serve as a model for retransplantation of autologous bone marrow in leukemic patients. In summary anti-T antibodies are powerful immunosuppressive agents if applied in vitro in connection with bone marrow transplantation. (no Refs)

80. IMMUNOCHEMOTHERAPY OF L1210 LEUKEMIA WITH AN ALPHA L1210 MONOCLONAL ANTIBODY (MEETING ABSTRACT).

Testorelli C, Panzeri P, Cantone V, Nicolin A

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Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

A monoclonal antibody (L 1) specifically directed against L1210 leukemia has been produced. Studies of in vitro characterization demonstrated that L 1 is an IgM immunoglobulin with a very high cytotoxic activity exclusively directed against the L1210 leukemia. Therefore L 1 has been considered for immunochemotherapeutic studies in a well known murine system. The results can be summarized as follows: 1) L 1 administered with rabbit complement is completely ineffective in the treatment of L1210 leukemic mice. 2) The therapeutic effect of cyclophosphamide is partially inhibited by L 1. 3) After iv administration, L 1 is capable of binding to the surface of tumor cells. 4) Tumor cells collected from L1210 bearing mice treated iv with L 1 are in vitro susceptible to lysis in presence of complement. 5) The free-cell ascites does not exhibit any anti-complementary activity. (no Refs)

81. PURIFICATION OF SPECIFIC ANTIBODY TO ALPHA-FOETOPROTEIN AND ITS IMMUNOLOGICAL EFFECT ON CANCER CELLS.

Hirai H, Tsukada Y, Hara A, Hibi N, Nishi S, Wepsic HT, Koji T, Ishii N

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J Chromatogr; 215:195-210 1981

Human or rat alpha-fetoprotein (AFP) was highly purified from ascitic fluid or serum of hepatoma bearers. The purification was carried out mainly by means of immunoadsorbent chromatography using Sepharose coupled to specific anti-AFP antibody with BrCN activation, and by Sephadex gel filtration. Horses were immunized with the purified AFP and the specific antibody was isolated from the antiserum by means of an immunoadsorbent coupled to purified AFP. The specific antibody was found to bind specifically wi th AFP-producing tumor cells. The antibody was applied for radio immunodetection of the tumor. 125I-labeled antibody was administered to patients or rats with hepatoma, and radioactivity localized in the tumors was scintiscanned with a scintillation camera. In this way, the location of the tumor was detected in about 50% of the hepatoma bearers. The cytotoxicity of the antibody was clearly demonstrated both in vitro and in vivo in animal experiments. The antibody was administered to patients with advanced hepatoma. Although no improvement of the disease was demonstrated, serum AFP levels decreased greatly and in some cases low AFP levels were maintained for long periods suggesting that the antibody suppressed AFP-producing hepatoma cells. No significant side effects were observed in patients who had been administered with the horse antibody. (Author abstract) (10 Refs)

ANIMAL MODELS OF BIOLOGICAL THERAPY

82. RETROVIRAL TREATMENT OF CANCER IN THE DOG: A NOVEL AND SUCCESSFUL IMMUNOTHERAPEUTIC APPROACH TO CURE OF CANCER IN OUTBRED SPECIES (MEETING ABSTRACT).

Huebner RJ, Trimmer RW, Bowles CA
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. The Association 187 pp., 1981.

A variety of retroviruses isolated from several strains of domestic and wild mice, cats, baboon, gibbon ape and squirrel monkey were grown in tumor, embryonic and thymic tissue cultures, following which the material was used unconcentrated or concentrated 1000X or higher, quick frozen and stored until used. The dogs treated had a variety of primary and metastatic cancers, diagnosed clinically and pathologically. The diagnoses included malignant lymphoma, lymphosarcoma, leukemia, mastocytoma, melanoma, hemangiosarcoma, urethral and testicular tumors, and carcinomas of mammary and thyroid origins. A wide variety of breeds were represented, including miniatures weighing less than 10 pounds up to a St Bernard of 150 pounds. Most were in the 50 pound range. All were pets referred by owners for treatment. Currently we can report 3 dogs that have been free of cancer for periods of 5, 8 and 11 mo, respectively. Others are in remission and are being followed for signs of relapse. Preliminary evidence indicates the mechanism of rejection to be strong cell-mediated immunity; dogs which failed to respond apeared to lack the capacity to mount an adequate immunological response. (no Refs)

CLINICAL IMMUNOLOGY

83. EVALUATION OF DIFFERENT METHODS FOR DETECTING CIRCULATING IMMUNE COMPLEXES. STUDIES IN PATIENTS WITH LUNG CANCER.

Fust G, Fekete B, Angyal I, Jakab A, Pal A, Meretey K, Falus A, Torok K, Szegedi G, Kavai M, Puskas E, Csecsi-Nagy M, Szabo T, Lenkey A, Misz M
Dept. Immunochemistry, Natl. Inst. Haematology and Blood Transfusion, Daroczi ut 24, P.O.B. 44, H-1502 Budapest, Hungary
J Immunol Methods; 46(3):259-276 1981

In a collaborative study involving 7 laboratories, sera from 53 patients with lung cancer, 37 primary and 16 secondary tumors, and sera of 40 healthy blood donors were tested by 19 different assays or assay modifications used for detecting immune complexes. In 12 out of 19 assays, significantly higher immune complex levels were found in the cancer patients than in the healthy subjects. Assays based on interactions between immune complexes and Fc receptors of different cells (lymphocytes, macrophages or platelets) discriminated between cancer patients and healthy subjects and a high percentage (47-87%) of positivity was observed in such assays in patients with lung cancer. In contrast, none of the tests based on immune complex-complement interactions discriminated between cancer patients and healthy subjects. Immunochemical analyses of the PEG precipitates obtained from the sera tested revealed that the concentrations of IgG, IgA and C3 were significantly higher in the precipitates obtained from patients' sera than from control sera, but no significant differences were seen in IgM and C1q concentrations. A 100% correct classification of individuals tested was obtained on discriminant analysis of results with 3 assays: EA rosette inhibition, ADCC inhibition and C3 concentration in PEG precipitates. Correlation between results obtained with individual sera by the different assays was very poor: significant correlation coefficients were found in only 13% of all possible paired comparisons. Our results suggest that Fc receptor-dependent assays are more suitable for detection and measurement of circulating immune complexes in lung cancer than tests based on interactions with complement. (Author abstract) (31 Refs)

84. ISOLATION OF LUNG CARCINOMA-ASSOCIATED ANTIBODIES FROM IMMUNE COMPLEXES AND PRODUCTION OF HETEROLOGOUS ANTISERA.

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Cancer Res; 42(1):292-300 1982

Immune complexes isolated from pleural effusions of lung carcinomas were dissociated by ion exchange chromatography in the presence of 8 M urea. The antibodies thus obtained from two lung adenocarcinomas and two squamous cell carcinomas were assayed by indirect immunofluorescence against a variety of target cells in fresh suspensions, tissue cultures, and paraffin-embedded sections. Strong cytoplasmic fluorescence was obtained with greater than 90% of the cell populations of all major histological types of lung carcinomas, and negative fluorescence was obtained with the cells of normal lung tissues and most of the nonpulmonary carcinomas. Antigen fractions prepared from the same lung carcinoma-associated immune complexes were used to immunize rabbits for the production of antisera directed against human lung carcinoma. The rabbit antibody preparations after proper absorptions were assayed in indirect immunofluorescence showing patterns of reactivity with normal and tumor cells of various derivations similar to those obtained with the human antibodies. Complete blocking of immunofluorescence staining with both allogeneic and xenogeneic antibody preparations was achieved by prior absorption with lung tumor tissue extracts or with various lung tumor antigen preparations. The present study demonstrates the isolation from lung tumor effusion immune complexes of antibodies with high affinity for lung carcinoma cells and of antigens that can be used to produce tumor-directed heterologous antibodies. The immunofluorescence staining of lung carcinoma-associated antigens in situ on paraffin-embedded sections provides new, topographical information. (Author abstract) (43 Refs)

85. PURIFICATION AND CHARACTERIZATION OF AN IMMUNOSUPPRESSIVE FACTOR FROM OVARIAN CANCER ASCITES FLUID.

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Eur J Immunol; 11(10):780-788 1981

A nonspecific immunosuppressive factor present in malignant (ovarian carcinoma) ascites fluid has been purified by acid extraction from a high mol wt (greater than 200,000) complex followed by preparative isoelectric focusing on Bio-lyte media. It is an acidic protein (pI = 3.6) of mol wt 50,000 to 52,000 as estimated by gel filtration and composed of subunits of 25,000 to 26,000 estimated by sodium dodecyl sulfate polyacrylamide gel electrophoresis, under reducing conditions. It inhibits the phytohemagglutinin-dependent mitogenic response of normal peripheral blood lymphocytes by 50% at 2 ug/ml concentrations in vitro and suppresses 80% of the plaque-forming cell response to sheep RBC at 100 ug per mouse in vivo. Its chemical identity with any of the known plasma proteins has not been established. Its failure to stain with periodic acid Schiff's reagent indicates its minimal content of carbohydrates. It is susceptible to tryptic and pronase digestion but insensitive to deoxyribonuclease and ribonuclease digestion. A smaller suppressive factor identified in the same fluid appears to be a lymphotoxin; it differs from the acid-extracted nonspecific suppressive factor in its lack of susceptibility to trypsin. (Author abstract) (31 Refs)

86. CELLULAR AND HUMORAL IMMUNITY IN HODGKIN'S DISEASE: I. PATIENTS IN CONTINUOUS LONG-TERM REMISSION.

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Scand J Haematol; 27(3):171-180 1981

Cell-mediated and humoral immunity to herpes simplex virus (HSV), cytomegalovirus (CMV) and varicella zoster virus (VZV) were examined in 37 patients with Hodgkin's disease in continuous long term remission. This group had lower blast-transformation than a matched control group to all three antigens. Patients originally showing B-symptoms had higher transformation to VZV than those with A-symptoms. Patients treated with irradiation only had higher transformation than those treated with either chemotherapy or a combination of chemotherapy and irradiation. There was a clear tendency towards lower transformation in patients having been in remission for 2 yr or less. Phytohemagglutinin (PHA) stimulation gave lower response in the patient group than in the control group. Patients with B-symptoms had lower response than those with A-symptoms. Interferon production was specially impaired in patients with B-symptoms. The patient group had higher CF titers against HSV and CMV while the control group had higher titers against VZV. B-symptom patients had higher titers against VZV than A-symptom patients. It is concluded that HD patients have impaired immune function many years after discontinuation of therapy, but there are certain differences regarding the in vitro immunity within the patient groups. (Author abstract) (17 Refs)

87. A NEW APPROACH TO THE IDENTIFICATION OF TUMOUR SPECIFIC ANTIBODIES IN PATIENTS WITH PANCREATIC CANCER (MEETING ABSTRACT).

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Newsletter Natl Pancreas Cancer Project; VI(2):18 1981

Human pancreatic tumor xenografts grown in athymic nude mice have been shown to shed components into the serum of these animals which evoke a specific antibody response against pancreatic cancer cells when the tumor-bearing mouse serum is injected into immunocompetent hairy littermates. The availability of the athymic Rowett nude rat (RNU/RNU) which we have recently shown to be a suitable model for the growth of human gastrointestinal tumors from both primary explants and cancer cells in tissue culture enabled a serial study of this phenomenon. Twelve nude rats were implanted with 3 x 10(7) pancreatic cancer cells; 8 tumors grew progressively. Blood (1.7 ml) was taken from the tail vein of each animal before implantation and thereafter every 21 days for up to 9 mo. Unlike the nude mouse, antibodies against tumor cells were detected in the serum of tumor-bearing rats using a quantitative I125 membrane binding assay, but an antibody response was detectable whether the tumor grew or did not grow. Carcinoembryonic antigen (CEA) and alpha fetoprotein (AFP) were measured serially in animals in which tumors grew. There was less than 4 ng/ml AFP in the serum of 4 tumor-bearing animals after 7 mo growth with tumors measuring 12 cm2. A progressive rise in CEA up to 156 ng/ml during 9 mo of growth was only detected in 1 of these 4 animals. Immunization of 4 immunocompetent rat hairy littermates with serum from 8 animals bearing 12 cm2 tumors elicited an antibody response selective against pancreatic cancer cells when compared with a panel of 5 other human tumor cell lines (binding ratio greater than 1.7) and normal human lymphocytes (binding ratio 4.8). Such selectivity was not detected in serum from tumor bearing animals (binding ratio less than 1.1), suggesting that immunization of hairy littermates may offer a biological opportunity for specific antibody production against pancreatic cancer cells. (no Refs)

88. HUMORAL IMMUNODEFICIENCY IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: POKEWEED MITOGEN-INDUCED GENERATION OF IMMUNOGLOBULIN-SECRETING CELLS (MEETING ABSTRACT).

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Exp Hematol; 9(Suppl9):86 1981

The common form of chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by an accumulation of monoclonal B lymphocytes. In the present study, using 45 patients with diagnosed B-CLL, we investigated the functional capacity of peripheral blood lymphocytes to transform into immunoglobulin-secreting cells (ISC). After stimulation with Pokeweed mitogen (PWM), ISC were enumerated in a reverse hemolytic plaque assay. Unseparated lymphocytes from 40 patients who had markedly increased numbers of peripheral blood cells were found to be unable to generate ISC in vitro thus indicating that the unseparated leukemic B cells cannot be activated. To exclude the possibility that the unresponsiveness was due to a relative dilution of T helper cells, isolated B cells from the patients were cultured together with T cells from normal subjects. These experiments revealed that the unresponsiveness is indeed caused by an intrinsic defect of the leukemic cells. On the other hand isolated T cells from CLL patients were found to be functionally normal helper cells when co-cultured with normal B lymphocytes. However, 5 patients who all had relatively low peripheral lymphocyte counts exhibited a significant response to PWM. Surprisingly, two of these patients had severe antibody deficiency. In these two patients, the effect of chemotherapy could be studied: the reduction of the peripheral lymphocytes resulted in a parallel and proportional increase in the number of ISC which was remarkably not followed by an increase in serum immunoglobulin levels. This finding suggests that a normal B cell population is present at least in some patients - thus indicating that the immunodeficiency which is characteristic for CLL is not always due to an absence of normal B lymphocytes, but to cellular or humoral immunosuppressive mechanisms. (no Refs)

89. ADJUVANT REACTIVITY PREDICTS SURVIVAL IN PATIENTS WITH HIGH-RISK PRIMARY MALIGNANT MELANOMA TREATED WITH SYSTEMIC BCG.

Cochran AJ, Buyse ME, Lejeune FJ, Macher E, Revuz J, Rumke P
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Int J Cancer; 28(5):543-550 1981

We report the prognostic importance of strength of reaction to BCG, tumor histology and clinical factors in patients with previously untreated high-risk (Clark, III, IV and V) primary malignant melanoma. One hundred and one such patients received high-dose BCG (1 x 10(8) viable units) by Heaf gun as an adjuvant to standardized primary surgery according to EORTC Protocol 18741. Univariate analysis of disease-free interval (DF) indicates that the degree of max reaction to BCG ($p = 0.0003$), Breslow thickness ($p = 0.0003$) and Clark level ($p = 0.002$) are highly significant prognostic factors. When a multivariate model using Cox's proportional hazard regression was used for DFI, the degree of max reaction to BCG and Breslow thickness were by far the most significant criteria. A prognostic equation was obtained to predict DFI from max BCG reaction and Breslow thickness. From analysis of the scores calculated in this way it appears that the two variables act independently. This technique permits the determination of values that are predictive of DFI and discriminate between subgroups of patients with different DFI characteristics (5 groups, p less than 0.0001). This exercise was repeated for survival and similar results were obtained. The degree of a patient's immune reaction to BCG administered therapeutically is of paramount importance in determining the likelihood of survival. This factor and the Breslow thickness can be integrated to produce a mathematical equation which accurately predicts survival for appropriately treated melanoma patients. (Author abstract) (25 Refs)

90. CHANGES IN THE SERUM ANTIBODY TITER OF PATIENTS GIVEN AUTOLOGOUS MELANOMA VACCINE DETERMINED BY THE IMMUNE ADHERENCE ASSAY METHOD AND THE DETECTION OF TUMOR ANTIGENS (MEETING ABSTRACT).

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Proceedings of the 9th Annual Meeting of Japan Society of Clinical Immunology held in Tokyo, 13-15 June, 1981. Japan Society of Clinical Immunology, Saitama Pref. 350-04, Japan, 239 pp., 1981.

Changes in the antibodies in the serum of patients before and after vaccine therapy against autologous melanoma cells, and the specificity of the increased antibody, were determined by absorption tests. The vaccine was prepared by x-ray irradiation of 2 x 10(7) tumor cells of patients with melanoma that had been serially cultured. The vaccine was used on the same patient every 3 wk in combin ation with BCG. The immune adherence assay was used as the serologic method. The antibody titer of a 53-yr-old female patient was increased from 4 to 32 after an autologous vaccine was given 5 x. The increased antibody was absorbed by cell lines of 8 of 12 melanomas in an absorption test, but it was not absorbed by other tumor cells, normal cells or heterologous cells. These results indicate that a melanoma antigen common to the antibody in her serum was detected. The antibody titer of another 58-yr-old female patient was increased from 4 to 128 after an autologous vaccine was given twice. Common antigens were found in the tissue culture cells used and in heterologous cells as well, by absorption tests. This antibody was thought to be an antibody against fetal calf serum used in the tissue culture. (no Refs) (In JPN)

91. SIGNIFICANCE OF SERUM IMMUNE COMPLEX ASSAY IN CANCER OF THE STOMACH AND COLON.

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Rinsho Meneki; 13(Suppl2):100-108 1981

This study represents an attempt to measure the circulating immune complexes in patents with cancer of the stomach or large intestine by the erythrocyte-amboceptor (EA) rosette inhibition test. The serum immune complex level determined by this method showed a significant correlation with that measured by the binding to surface receptors of cultured lymphoblasts (Raji cells) and a significant inverse correlation with the serum complement level (CH50). It did not correlate with the phytohemagglutinin skin test or lymphocytic blastogenesis assay, whereas the IgG.FcR+ T cell percentage was low in patients showing a high serum level of immune complexes. Clinically, circulating immune complexes were demonstrated in 66.7% of untreated patients with gastric carcinoma and 82.5% of those with carcinoma of the colon, in contrast with 5.9% in normal controls. Of these patients, those who received a curative operation and those who underwent immunochemotherapy and/or local continuous ia infusion with anticancer drugs displayed a significant decrease in circulating immune complexes. The results indicate that serum immune complexes can be measured by the EA rosette inhibition test; that there appears to be no correlation between the serum immune complex level and nonspecific cellular immune responsiveness; and that the IgG.FcR+ T cell percentage is not correlated with the serum concentration of the immune complexes but the data obtained suggest the presence of immune complexes attached to IgG.FcR+ T cells. (26 Refs) (In JPN)

92. SEVERE ACQUIRED IMMUNODEFICIENCY IN MALE HOMOSEXUALS, MANIFESTED BY CHRONIC PERIANAL ULCERATIVE HERPES SIMPLEX LESIONS.

Siegal FP, Lopez C, Hammer GS, Brown AE, Kornfeld SJ, Gold J, Hassett J, Hirschman SZ, Cunningham-Rundles C, Adelsberg BR, Parham DM, Siegel M, Cunningham-Rundles S, Armstrong D
Mt. Sinai Medical Center, New York, NY, 10029
N Engl J Med; 305(24):1439-1444 1981

Cellular immunodeficiency associated with chronic perianal ulcerative herpes simplex lesions is reported in four homosexual men. Onset of the disease was characterized by malaise, fever, and wt loss. Later infections included cytomegalovirus, Pneumocystis carinii, and Candida albicans. One patient developed Kaposi's sarcoma. Skin anergy, lymphopenia, poor or absent responses to plant lectins and antigens in vitro, and depressed natural killer cell activity against target cells infected with herpes simplex virus were observed. An association may exist between primary cytomegalovirus infection and a particularly prolonged cellular immunodeficiency state. (29 Refs)

93. PNEUMOCYSTIS CARINII PNEUMONIA AND MUCOSAL CANDIDIASIS IN PREVIOUSLY HEALTHY HOMOSEXUAL MEN. EVIDENCE OF A NEW ACQUIRED CELLULAR IMMUNODEFICIENCY.

Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A
Dept. Medicine, UCLA Sch. Medicine, Center for the Health Sciences, Los Angeles, CA, 90024
N Engl J Med; 305(24):1425-1431 1981

An acquired T-cell immunodeficiency is reported in four previously healthy homosexual men. All patients experienced malaise, fever, and lymphadenopathy for several mo prior to onset of more specific symptoms. All contracted Pneumocystis carinii pneumonia, extensive mucosal candidiasis, and multiple viral infections. Cytomegalovirus was found in the secretions of all patients, and Kaposi's sarcoma developed in one patient 8 mo after he presented with esophageal candidiasis. Antibodies to Epstein-Barr virus and hepatitis B were detected in the other three. Monoclonal-antibody analysis of peripheral blood T-cell subpopulations revealed an inversion of the T helper to suppressor/cytotoxic ratio. The association between chronic cytomegalovirus infection and Kaposi's sarcoma is discussed, and a relationship between the immunodeficiency syndrome and the recent appearance of Kaposi's sarcoma in the male homosexual population is suggested. Cytomegalovirus infection could be a result rather than a cause of the T-cell defect; exposure to an undetected microorganism, drug, or toxin may have made these patients susceptible to infection by opportunistic organisms including cytomegalovirus. (41 Refs)

94. INTERFERON-INDUCED NK AUGMENTATION IN HUMANS. AN ANALYSIS OF TARGET RECOGNITION, EFFECTOR CELL RECRUITMENT AND EFFECTOR CELL RECYCLING.

Ullberg M, Merrill J, Jondal M
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Scand J Immunol; 14(3):285-292 1981

By combining a single-cell cytotoxicity assay in agarose with estimations of the max natural killer (NK) cell potential (Vmax) by 51Cr release, the mechanisms behind interferon augmentation of human NK cells were analyzed. The number of target-binding cells (TBCs) the fraction of active TBCs, and NK cell recycling were studied after short-term interferon treatment. The results demonstrate a dual effect of interferon on human NK cells: effector cell recruitment and increased effector cell recycling. Both of these variables were increased when NK cells were tested against the standard target K-562 and against Daudi and BJAB cells, derived from B-type lymphomas. However, when T cell lines derived from acute lymphocytic leukemia (Molt-4 and 1301) were used as targets, a larger fraction of active NK cells were found among untreated TBCs, whereas interferon treatment only resulted in increased effector cell recycling and not in effector cell recruitment. No increase in TBCs after interferon treatment could be detected with any cell line tested. The difference seen between T and non-T cell lines with regard to interferon-induced effector cell recruitment is discussed in relation to known characteristics of the human NK system. (Author abstract) (32 Refs)

95. IMMUNOLOGIC ABNORMALITIES IN MYELOFIBROSIS WITH ACTIVATION OF THE COMPLEMENT SYSTEM.

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Blood; 58(5):904-910 1981

Eighteen patients with agnogenic myeloid metaplasia with myelofibrosis were studied for clinical and laboratory evidence of immunologic dysfunction. Clinical findings included the presence of arthritis, vasculitis, and erythema nodosum. Laboratory abnormalities included the presence of circulating immune complexes, antinuclear antibodies, positive direct Coombs tests, elevated latex fixations, and a circulating lupus type anticoagulant. Total hemolytic complement was markedly depressed in four patients. Analysis of complement (C) components C1-C9 and factor B demonstrated significant reduction of only C3 and factor B. By crossed-immunoelectrophoresis, both C3 and factor B, but not C4, were cleaved, indicating that C activation was occurring predominantly via the alternative pathway. The control protein beta1H and C3b inactivator were decreased in three of four patients with hypocomplementemia. These three patients subsequently developed systemic infections that contributed to their cause of death. These data suggest that immunologic mechanisms associated with activation of the complement system play an important role in the disease process of some patients with agnogenic myeloid metaplasia with myelofibrosis. (Author abstract) (36 Refs)

96. NATURAL CYTOTOXICITY AND INTERFERON PRODUCTION IN HUMAN CANCER: DEFICIENT NATURAL KILLER ACTIVITY AND NORMAL INTERFERON PRODUCTION IN PATIENTS WITH ADVANCED DISEASE.

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Dept. Pathology, Albert Einstein Coll. Medicine, 1300 Morris Park Ave., Bronx, N Y, 10461
J Immunol; 127(5):1817-1822 1981

Natural cytotoxicity was measured in 51 adult patients with solid epithelial malignant tumors and in 27 normal subjects. Peripheral blood leukocytes (PBL) from 31% of the patients and 7% of the controls failed to kill target cells (K562) in a short-term chromium-release assay. When patients were classified according to clinical stage, PBL from 12% of patients with localized cancers, but 50% of patients with advanced disease, failed to exhibit cytotoxicity within the normal range. Pretreatment of PBL with interferonalpha (IFNalpha) or with Newcastle Disease Virus (NDV), a potent inducer of IFNalpha, enhanced cytotoxicity from all normal subjects. Of patients whose PBL lacked spontaneous cytotoxicity, half were able to kill normally after pretreatment of PBL with IFNalpha or NDV. Virtually all the patients whose PBL were unable to kill despite pretreatment with IFNalpha or virus had disseminated malignancies. IFNalpha production by PBL exposed to NDV and to K562 cells was normal in all the patients regardless of stage of disease or ability to kill K562 cells. The observed defect in natural cytotoxicity is thus unlikely to be due to a failure of PBL to produce IFNalpha. (Author abstract) (32 Refs)

REVIEWS

97. CANCER IMMUNOTHERAPY. REALITY OR FICTION?.

Belpomme D, Marty M, Gisselbrecht C, Mignot L, Pujade-Lauraine E
Departement d'Hematologie et d'Oncologie, Hopital Saint-Louis, 2, place du Docteur-Fournier, 75475 Paris, France
Sem Hop Paris; 57(37/38):1547-1556 1981

Recent clinical studies on immunotherapy in cancer are reviewed, and future possibilities for the use of immunotherapy in cancer treatment are discussed. The most important nonspecific immunomodulators are BCG, Corynebacterium parvum (C. parvum) and levamisole. Indications for immunotherapy are residual cancer following the complete reduction of tumor vol by traditional methods and leukemias and lymphomas after achieving complete remission through radiation or chemotherapy. Of 54 clinical studies reviewed, 23 achieved positive immunotherapeutic results. There have been no positive randomized trials with C. parvum. The dose and route of administration have been proven significant. BCG given systemically was rarely effective whereas it is much more active when given locally. When levamisole was given po alone or with chemotherapy, its effectiveness was not dependable. Cancers which responded to immunotherapy included melanomas, bronchial carcinomas and residual or metastatic breast cancers. In order to use immunotherapy in a rational manner, the origin, doses, and routes of administration of the various immunomodulators must be standardized. Examples of immunomodulators currently being tested are extracts of Brucella pertussis, ribosomal particles from Klebsiella pneumoniae, tuftsin, lysophospholipids, lipid amines, biostim, azimex on, an isoprinosine analogue, and cyclomunine. (39 Refs) (In FRE)

98. IMMUNE COMPLEXES AND CANCER - UNMASKING THE HIDDEN HUMORAL IMMUNE RESPONSE TO NEOPLASTIC TISSUE.

Rossen RD
Dept. Developmental Therapeutics, Univ. Texas M. D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 33(5):221-226 1981

A paradox seen in cancer is that plasma from tumor-bearing individuals, even when it contains antitumor antibody, may facilitate tumor growth. Methods of detecting soluble immune complexes (SIC) in sera and other body fluids, and their composition in cancer, are discussed. Biologic effects of CIS are discussed as well as circulating immune complexes and the mononuclear phagocyte system. CIS may have profound effects on cells such as suppression of of recruitment of new antigen-reactive lymphocytes and interference with Fc receptor function of mononuclear lymphoid cells. A prime reason to differentiate whether SIC in sera contain tumor-associated antigens or anti-idiotypes is to improve understanding of how immune complex formation influences regulation of host response to tumors. Operating on the assumption that CIS may be detrimental, attempts at their removal has resulted in claims of benefit in treatment of cancer. Unblocking of hidden tumor-specific cytotoxins also may be a major effect of therapy designed to remove soluble complexes from plasma. Very little is known about the composition and effects of SIC in patients with malignant diseases. (24 Refs)

99. ASSAYS OF IMMUNOCOMPETENCE IN THE STAGING AND PROGNOSIS OF CANCER.

Robinson JC
Dept. Surgery, Veterans Admin. Medical Center, Baltimore, MD
Surg Gynecol Obstet; 153(6):909-921 1981

There are definite immunologic abnormalities associated with the cancer bearing state which are apparent on both in vitro and in vivo testing. The wt of evidence presented suggests an increasing loss of immunocompetence with increasing disease stage and a degree of positive correlation of immunologic responsiveness with prognosis. Unfortunately the correlation is not absolute for any one individual, although it is often fairly well defined for a large group of patients. This is a failure of all other prognostic studies as well. The critical question as to whether or not this loss of immune integrity reported represents a cause or a result of cancer progression remains largely unanswered. The data suggests that the measured impairment of immunologic responsiveness stems from conditions brought about by the tumor bearing state. Regardless of which precedes the other, the cancer or the immunoincompetence, the additional question as to the effect of immune impairment on the disease progression also remains uncertain. Results of tests to monitor immunocompetence appear to be of some value if used as additional data on which to base prognostic conclusions. Dinitrochlorobenzene skin testing is an assay that is easily performed and probably yields the most easily obtained significant prognostic information. (Author abstract) (97 Refs)

100. DEPRESSED IMMUNITY AND THE DEVELOPMENT OF CANCER.

Penn I
Dept. Surgery, Univ. Colorado Health Sciences Center, 1055 Clermont St., Denver, CO, 80220
Clin Exp Immunol; 46(3):459-474 1981

Epidemiological, clinical, and experimental studies of depressed immunity and cancer are reviewed. Topics include transplantation of tumors, cancer in patients with naturally occurring immunodeficiency disorders, de novo cancer in organ transplant recipients, and cancer in uremic patients. Patients with autoimmune and other diseases treated with immunosuppressive agents have increased cancer incidence. Second cancers, particularly leukemias, are more frequent in patients treated with chemo- and radiotherapy. Disturbances in immunity as causes of cancer are presented; immune surveillance, immune stimulation, chronic antigenic stimulation, defective immunoregulation, spontaneous regression of lymphomas, interferons, oncogenic viruses, oncogenic and co-oncogenic effects of immunosuppressive and cancer therapeutic agents, and other potentially oncogenic treatments (UV and arsenic for psoriasis) are discussed. Animals and patients vary in their susceptibility to oncogenic stimuli. Evidence suggests that the immune system plays a key role in host defense against cancer, but many unanswered questions remain. (149 Refs)

101. OPPORTUNISTIC INFECTIONS AND KAPOSI'S SARCOMA IN HOMOSEXUAL MEN.

Durack DT
Duke Univ. Medical Center, Durham, NC, 27710
N Engl J Med; 305(24):1465-1467 1981

Current data and theories concerning opportunistic infections and Kaposi's sarcoma in homosexual men are reviewed. Patients are typically young and live in large cities, and many use drugs. Infectious agents are low grade pathogens that often cause opportunistic infections in compromised hosts, and the death rate is very high. The immunodeficiency is cellular rather than humoral, and the gap in host defenses is not limited to those against any one class of microbe. Evidence of previous or current cytomegalovirus infection is a common finding. Kaposi's sarcoma is found in young Africans, elderly Americans, renal-transplant recipients, and homosexual men. The discovery of cytomegalovirus genome in Kaposi's sarcoma tissue indicates the possibility of a cause-effect relationship between the virus and the tumor; some new factor may have distorted the host-parasite relation. Recreational drugs such as amyl nitrite may combine with the effects of persistent viral infection to cause immunosuppression in some genetically predisposed men. (16 Refs)

102. IMMUNODEFICIENCIES IN HODGKIN'S DISEASE. PART I: T CELL-MEDIATED IMMUNITY.

Gupta S
Clinical Immunology Service, Sloan-Kettering Inst., New York, NY
Clin Bull; 11(2):58-65 1981

The association between Hodgkin's disease and immunodeficiency states is reviewed. Immunodeficiencies may predispose patients with Hodgkin's disease to a second neoplasm and to increased risk of infectious complications, especially viral and fungal (eg herpes zoster and cryptococcosis). Both in vivo and in vitro T cell-mediated immune responses in patients with various stages of Hodgkin's disease are discussed, including delayed type hypersensitivity, homograft rejection, lymphocyte response to soluble antigens and to mitogens and allo-antigens, analysis of T cells and T cell subsets, and cytotoxic response and mechanisms responsible for T cell-mediated immunodeficiencies. The role played by splenectomy in treatment of Hodgkin's disease is discussed. (71 Refs)

103. IMMUNOPHARMACOLOGICAL EFFECTS OF IRRADIATION.

Serrou B, Rey A
Laboratoire d'Immunopharmacologie des Tumeurs, INSERM U 236, ERA-CNRS no. 844, Centre Paul Lamarque, B.P. 5054, F-34033 Montpellier Cedex, France
Cancer Immunol Immunother; 11(4):239-242 1981

Effects of irradiation on immune response are reviewed. Localized irradiation has a depressive effect on T lymphocytes, monocytes, and null cells. Decreases in mitogen response, natural killer activity, and antibody- and phytohemagglutinin-induced cytotoxic response are produced. B lymphocyte response is apparently not affected, at least in the short term. Animal studies indicate a decrease in specific T cell cytotoxicity against tumor antigens, but the decrease has not been demonstrated in man. Preliminary results show that autologous rosette formation decreases after irradiation, indicating change in a nonsuppressor T cell population. Stress effects have been produced in animals at doses ranging from 0.12 to 16 gray local irradiation. Irradiation may combine with other agents to promote development of certain cancers. Some controversial studies suggest that irradiation itself may promote metastasis. The negative effects of irradiation may be reducible or avoidable by the use of other appropriate agents such as BCG. Clinical studies are required to determine the effects of irradiation on humans. (49 Refs)

104. EXPLOITATION OF MONOCLONAL ANTIBODIES: A 'WHO'S WHO' OF HAEMOPOIETIC MALIGNANCY.

Greaves MF, Delia D, Robinson J, Sutherland R, Newman R, Moore MA, Lajtha L, Gallo R, McCulloch EA, Boggs D, Sachs L
Imperial Cancer Res. Fund Laboratories, POB 123, Lincoln's Inn Fields, London WC2A 3PX, England
Blood Cells; 7(2):257-280 1981

A panel of monoclonal antibodies plus other conventional markers (such as anti-terminal deoxynucleotidyl transferase) were used to explore detailed phenotypes of leukemic cells in relation to normal hemopoietic differentiation. Consistent, composite phenotypes of different subclasses of lymphoid malignancies closely mimic those of corresponding normal cells at equivalent stages of differentiation. The study indicates three major target cell populations are available for lymphoid malignancy: the pluripotential stem cell; lymphoid progenitors or stem cells in bone marrow; and long-lived, mature and immunocompetent T and B cells. The major phenotypes in different leukemias represent the level of 'maturation arrest' imposed on the dominant subclone; this is determined by, but not necessarily synonymous with, the 'target cell' and associated clonogenic cell population in the leukemia. No consistent major abnormalities of gene expression were found; while such may exist, it is suggested that they are irrelevant to the central issue of what alterations are essential and sufficient for the evolution of clonogenic leukemic cells. It is proposed instead that subtle changes, which uncouple proliferation and differentiation, are all that is required. (77 Refs)

105. CONTRIBUTIONS OF HYBRIDOMA TECHNOLOGY TO CANCER IMMUNOLOGY.

Allison JP
Res. Div., Univ. Texas Science Park, Smithville, TX
Cancer Bull; 33(5):226-232 1981

In connection with the development of the hybridoma technique for the generation of monoclonal antibodies, discussions are presented of the demonstration and characterization of tumor-associated antigens, classification of lymphoid tumors, immunodiagnosis of cancer, and immunotherapy. While these monoclonal antibodies have been most extensively studied in melanoma cells, they have also been detected in colorectal carcinoma, neuroblastoma, glioma, breast carcinoma, and leukemia. The antigens involved and their distribution, are reviewed. The availability of monoclonal antibodies to specific leukemia-associated antigens and to T-cell differentiation antigens has provided tools to assess further the heterogeneity of lymphoid tumors. Monoclonal antibodies have provided incisive probes for the detection and diagnosis of cancer. They offer the promise of a major new weapon, the targeted toxin, among weapons to use against cancer. This new era promises to be the renaissance of tumor immunology. (54 Refs)

106. MONOCLONAL ANTIBODIES IN CLINICAL IMMUNOLOGY.

Sevier ED, David GS, Martinis J, Desmond WJ, Bartholomew RM, Wang R
Hybritech, Incorporated, 11085 Torreyana Rd, San Diego, CA, 92121
Clin Chem; 27(11):1797-1806 1981

Advances in clinical immunodiagnostics resulting from the application of hybridoma technology are starting to appear. Monoclonal antibodies are beginning to displace their antiquated progenitors, polyclonal antisera, in many facets of immunology. Their homogeneity, specificity, and availability make hybridoma-derived antibodies the immunological reagents of the future in immunoassays, immuno-affinity chroma tography, immunotherapy, and areas yet to be defined. (Author abstract) (206 Refs)

107. USE AND ABUSE OF LABORATORY TESTS IN CLINICAL IMMUNOLOGY: CRITICAL CONSIDERATIONS OF EIGHT WIDELY USED DIAGNOSTIC PROCEDURES.

IUIS/WHO Working Group
(c/o G. Torrigiani) Immunology Unit, World Health Organization, 1211 Geneva 27, Switzerland
Clin Exp Immunol; 46(3):662-674 1981

A review is presented of methodological considerations and clinical indications for quantitation of immunoglobulins (serum electrophoresis, quantitation of major immunoglobulin classes, and immunoelectrophoresis), immunoelectrophoretic analysis of immunoglobulins in biological fluids, measurement of total and specific IgE, complement measurements, detection of immune complexes in human biological fluids, detection of autoantibodies by indirect immunofluorescence, B and T cell determination, and analysis of lymphocyte response to mitogens in the evaluation of cell-mediated immunity. (6 Refs)

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CLINICAL CANCER IMMUNOLOGY AND IMMUNOTHERAPY

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CLINICAL TRIALS

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HE 20. 3173/2:

1. FOLLOW-UP RESULTS FROM A RANDOMIZED TRIAL FOR T3 AND T4 BREAST CANCER PATIENTS: PREVIOUS BCG IMMUNOTHERAPY IMPROVES RESPONSE TO CHEMOTHERAPY IN THE RELAPSE PATIENT.

Serrou B, Sancho-Garnier H, Cappelaere P, Plagne R, Metz R, Schneider M, Chollet P, Namer N, Pujol H, Gary-Bobo J, Meyer G, Mathe G

Centre Paul Lamarque, Dept. Immuno-Chemotherapy, Hopital Saint-Eloi, F-34033 Montpellier Cedex, France

Recent Results Cancer Res; 80:157-161 1982

Following locoregional treatment, patients were randomized into three groups: The first group received no complementary treatment; the second group received adjuvant chemotherapy (vincristine, cyclophosphamide, and 5-fluorouracil once a mo for 12 mo); and the third group was treated by immunotherapy (150 mg BCG once a wk for 1 yr). Sixty-two of the 82 patients studied were menopausal. No significant difference was observed between the three groups. All patients were followed-up for at least 18 mo. The disease-free interval difference between the chemotherapy group and the control and immunotherapy groups is not significant. But it should be noted that only 21.8% of the control group did not relapse compared to 57% in the chemotherapy group. BCG immunotherapy in such patients must be considered ineffective. However, our results suggest that patients first treated with BCG respond better to chemotherapy than patients not receiving any previous therapy. (Author abstract) (22 Refs)

2. ADJUVANT CHEMOIMMUNOTHERAPY WITH LMF PLUS BCG IN NODE-NEGATIVE AND NODE-POSITIVE BREAST CANCER - INTERMEDIATE REPORT AT 4 YEARS.

Senn HJ, Amgwerd R, Jungi WF, Hochuli R, Ammann J, Engelhart G, Heinz C, Wick A, Enderlin F, Creux G, Simon B, Lanz R, Bigler R, Seiler S

Kantonsspital, Oncology Center, CH-9007 St. Gallen, Switzerland

Recent Results Cancer Res; 80:177-184 1982

A randomized surgical adjuvant trial in 242 evaluable patients with T1-3a, N0-1, and M0 breast cancer was initiated 4 yr ago. The well-tolerated, oral combination chemotherapy with six cycles of Leukeran plus methotrexate plus fluorouracil (LMF) plus repeated BCG skin scarifications was used. After 4 yr, the following results were seen: (1) significant increase of relapse-free (RFS) and also overall survival (S) in both pre- and postmenopausal node-negative patients versus surgical controls (RFS 91.1 vs 70.1%, $p = 0.003$; S 96 versus 88%, $p = 0.03$); (2) no significant increase of RFS or S in pre- and postmenopausal node-positive patients versus surgical controls (RFS 50.1 versus 44%, $p = 0.49$; S 70 versus 68%, $p = 0.9$, respectively); (3) Patients receiving greater than 90% of the planned LMF dose showed significantly better survival after 4 yr; and (4) Nonrandomized comparison with concurrent Swiss adjuvant studies with LMF alone indicate no beneficial or harmful effect of BCG skin scarifications in addition to the six-cycle LMF. (Author abstract) (11 Refs)

3. ADJUVANT INTERMITTENT CHEMOIMMUNOTHERAPY FOR PRIMARY BREAST CANCER: A PROSPECTIVE STUDY WITH IMMUNOLOGIC FOLLOW-UP.

Betzler M, Schreml W, Lang M, Lohrmann HP, Flad HD, Schlag P, Herfarth C, Heimpel H
Dept. fur Chirurgie, Universitat Ulm, Steinhovelstrasse 9, D-7900 Ulm, W. Germany
Recent Results Cancer Res; 80:185-191 1982

In an interdisciplinary prospective study 50 patients surgically treated for breast cancer were treated with six monthly courses of aggressive adjuvant chemotherapy (adriamycin and cyclophosphamide) and were randomized to receive either immunotherapy with levamisole or no additional therapy. Probability of disease-free survival for the whole group is 54.9% at 42 mo. There was no noticeable difference in disease-free survival for either pre- and postmenopausal women or for patients treated with or without levamisole. The addition of levamisole had no effect on the depression of in vitro immunologic functions during chemotherapy. (Author abstract) (9 Refs)

4. HAIRY CELL LEUKEMIA: CLINICAL EFFECTS OF THE METHANOL EXTRACTION RESIDUE (MER) OF BCG, LITHIUM CARBONATE AND MONONUCLEAR CELL-ENRICHED LEUKOCYTE TRANSFUSIONS.

Quesada JR, Hersh EM, Keating M, Zander A, Hester J
Dept. Developmental Therapeutics, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Leuk Res; 5(6):463-476 1981

The effect of mononuclear cell-enriched WBC transfusions (MNCTs) alone or in combination with iv methanol extraction residue (MER) was studied in 11 men (37-61 yr old) who had hairy cell leukemia (HCL). The combination of MER an lithium carbonate (LC) also was examined. Of eight patients receiving the MER alone, two had a minimal hematologic response (MHR). Of four patients receiving LC and MER, one showed an MHR. Of seven evaluable patients who received MNCTs, four achieved a response (2 complete and 2 partial). The incidence of infection observed after therapy did not differ significantly from that observed before therapy. Side effects of the MER treatment included fever (usually lasting 24 hr), chills and malaise, mild dyspnea or dry cough, and polyarthralgia. Side effects of the LC treatment included dizziness, distal tremor and lightheadedness. Two patients developed acute maculopapular rash in association with the MNCT treatment. The results indicated that favorable hematological effects can be produced following hematopoietic manipulation intended to enhance proliferation and maturation of bone marrow precursor cells. (51 Refs)

5. 11. THE FINNISH LEUKAEMIA GROUP: LEVAMISOLE IN MAINTENANCE THERAPY OF ACUTE MYELOID LEUKEMIA IN ADULTS.

Lehtinen M, Ahrenberg P, Hanninen A, Ikkala E, Lahtinen R, Levanto A, Palva I, Rajamaki A, Rosengard S, Ruutu T, Sarna S, Selroos O, Timonen T, Waris E, Wasastjerna C, Vilpo J, Vuopio P
Tampere Central Hosp., SF-33520 Tampere 52, Finland
Recent Results Cancer Res; 80:70-72 1982

The Finnish Leukemia Group has carried out a randomized, multicenter trial to study the effect of levamisole on the remission maintained with 6-mercaptopurine and methotrexate in acute myeloid leukemia in adults. Levamisole was given on 3 consecutive days every 2 wk. Twenty-five patients received only chemotherapy, while 26 patients received levamisole as well. The patients receiving levamisole showed significantly better remission duration than those given only chemotherapy (p = 0.033, Mantel's summary X(2)-test). There are four long term survivors in the levamisole group versus none in the chemotherapy group. The remissions have lasted 48-75 mo. (Author abstract) (8 Refs)

6. 8. THERAPEUTIC EFFECTIVENESS OF NEURAMINIDASE-TREATED ALLOGENEIC MYELOBLASTS AS IMMUNOGEN IN ACUTE MYELOCYTIC LEUKEMIA.

Bekesi JG, Holland JF

Dept. Neoplastic Diseases, City Univ. New York, Mount Sinai Sch. Medicine and Hosp., New York, NY, 10029

Recent Results Cancer Res; 80:42-55 1982

Our chemoimmunotherapy study shows significantly longer remission and survival in acute myelocytic leukemia (AML) patients who have been immunized with neuraminidase-treated allogeneic myeloblasts as compared to patients who received chemotherapy alone or neuraminidase-treated myeloblasts plus MER. MER impairs the immunotherapeutic effectiveness of neuraminidase-treated allogeneic myeloblasts in AML patients. The in vivo and in vitro immunologic status in each arm of the protocol correlate well with the duration of remission and survival of the patient. (Author abstract) (22 Refs)

7. RANDOMIZED CLINICAL TRIAL OF IMMUNOTHERAPY AND ANDROGENOTHERAPY FOR REMISSION MAINTENANCE IN ACUTE NON-LYMPHOCYTIC LEUKEMIA.

Mandelli F, Amadori S, Dini E, Grignani F, Leoni P, Liso V, Martelli M, Neri A, Petti MC, Ferrini PR

Istituto di Ematologia, Universita di Roma, Via Chieti 7, 00161 Rome, Italy

Leuk Res; 5(6):447-452 1981

A randomized study of 212 consecutive, previously untreated acute nonlymphocytic leukemia (ANLL) patients was conducted to determine if the addition of BCG and/or stanozolol (STZ) to cyclic chemotherapy (CT) produces longer remissions than maintenance with CT alone. All patients received the same induction CT (daunomycin, cytarabine, and thioguanine; 3 courses). When complete remission was achieved, the patients received consolidation CT (adriamycin and cytarabine; alternating courses; 2 mo). Patients who were in complete remission at the end of consolidation CT were allocated to one of four therapy regimens: CT alone (A), CT plus BCG (B), CT plus STZ (C), or CT plus BCG and STZ (D). Eighty-two patients (42 males, 40 females; 7-74 yr old) were randomized to the maintenance arms. The median duration of remission was 64 wk for regimen A, 65 for B, 42 for C, and 54 for D, the the differences between the remission duration curves were not statistically significant. Five patients (2 in regimen B, 1 in each of regimens A, C, and D) completed therapy and were in remission 12 mo after discontinuing therapy. Fifty-six relapses (51 bone marrow, 1 CNS, 1 skin, 1 testis, and 1 breast) were reported. The median survival for the 82 randomized patients was 92 wk. Toxic manifestations to therapy are described. The results indicated that BCG immunotherapy and/or androgenotherapy used in combination with maintenance CT does not prolong the duration of remission. (28 Refs)

8. 15. MAINTENANCE IMMUNOTHERAPY WITH BCG IN NON-HODGKIN'S MALIGNANT LYMPHOMAS: A PROGRESS REPORT OF A RANDOMIZED TRIAL.

Hoerni B, Durand M, Eghbali H, Hoerni-Simon G, Richaud P, De Mascarel A

Fondation Bergonie, 180 rue de Saint-Genes, F-33076 Bordeaux Cedex, France

Recent Results Cancer Res; 80:92-97 1982

Ninety-eight patients with non-Hodgkin's malignant lymphoma were first put into complete remission by a combination of chemotherapy and radiotherapy, and then received one course of chemotherapy as reinforcement. They were then randomized to receive either maintenance BCG therapy or no other treatment. Ninety-three patients were available for this analysis. There was a significant difference (p = 0.021) in relapse-free survival times between the two groups of patients. This difference is particularly significant in male patients, in patients ages 50-65 yr, in all histologic classes, in patients treated after an initial relapse, and in clinical Stages I and II . There was also a difference in crude survival, but the difference was not significant. (Author abstract) (7 Refs)

9. ASPECIFIC IMMUNOTHERAPY IN UNRESECTABLE LUNG CANCER (MEETING ABSTRACT).

Liberati AM, Borden EC, Voelkel J, Coates A

Department of Human Oncology, University of Wisconsin, Madison, WI, 53792

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Fifty-nine patients with unresectable lung cancer (Stage III AJC staging criteria) all of histologic types were treated with combination chemotherapy with or without radiotherapy and randomized to receive no additional therapy, immunotherapy with BCG, or levamisole. Sixteen patients had limited disease (tumor confined to one hemithorax and ipsilateral mediatinal nodes) and received both radiation therapy and chemotherapy. Forty-three patients had extensive disease (tumor spread beyond the sites indicated above). Combination chemotherapy (CCM) administered in 8 wk cycle consisted of lomustine (CCNU) 70 mg/m2 po on day 1, cyclophosphamide 500 mg/m2 iv and methotrexate 15 mg/m2 iv on days 1, 8, 29 and 36. BCG (Tice strain) by the tine technique was given every two wk during radiation therapy and then on days 15, 22, 43 and 50. Levamisole 100 mg/m2 po was administered for 3 consecutive days every 2 wk during radiation therapy and then for 2 consecutive days for 6 wk of each chemotherapy cycle. Cell type, disease extent and performance status (PS) were well balanced in the three randomization arms. Objective response and stabilization rates were correlated with the extent of disease. Time to progression and survival were significantly influenced by initial PS and disease extent. Prolongations of time of progression and survival time for patients receiving immunotherapy over controls were observed although neither was statistically significant. Although a trend toward benefit of combined chemotherapy and levamisole existed this did not reach statistical significance. Based upon statistical estimates, a trial of patients would be required to demonstrate significant benefit from this treatment program. (no Refs)

10. SPECIFIC ACTIVE IMMUNOTHERAPY IN LUNG CANCER: THE INDUCTION OF LONG-LASTING CELLULAR RESPONSES TO TUMOUR-ASSOCIATED ANTIGENS.

Stewart TH, Hollinshead AC, Harris JE, Raman S
Univ. Ottawa, Sch. Medicine, Ottawa, Ontario, Canada
Recent Results Cancer Res; 80:232-239 1982

Specific active immunotherapy (IT) was tested in patients with lung cancer (LC). Following surgical resection of the lung, patients were given skin tests with soluble, allogeneic tumor-associated antigens (TAA) derived from squamous cell carcinoma, adenocarcinoma, and anaplastic large- and small-cell carcinoma. Antigen dose was 100 ug in 0.1 ml. Twelve patients did not receive IT. Of these, seven showed weak to moderate skin reactions and one died of LC after 7 mo. Of five patients who showed reactions to bacterial antigens but not TAA antigens, four died of LC after 2-23 mo. Eleven patients received IT, all of whom showed strong positive skin reactions to TAA. Two of these died of LC 13-32 mo after testing. Nine patients received IT and methotrexate chemotherapy (CT). One of these died of metastases 4 mo after testing; another died of noncancerous causes 26 mo after testing. Two-yr survival rates were 96% for patients receiving IT or IT plus CT and 72% for nonimmunized controls. Four-yr survival rates were 80% for IT and IT plus CT and 50% for controls. Patients receiving IT plus CT showed better survival after 36 mo than those receiving only IT. IT produced delayed hypersensitivity which lasted 5 yr or more. Results suggest that prophylactic IT might reduce cancer incidence among high-risk populations. (9 Refs)

11. INTERIM RESULTS OF EORTC PROTOCOL 08742: COMPARISON, AFTER IRRADIATION OF LOCALLY ADVANCED SQUAMOUS CELL BRONCHIAL CARCINOMA OF ABSTENTION, IMMUNOTHERAPY, COMBINATION CHEMOTHERAPY, OR CHEMOIMMUNOTHERAPY.

Israel L, Depiere A, Dalesio O
Hopital Avicenne, Bobigny, France
Recent Results Cancer Res; 80:214-218 1982

After irradiation of locally unresectable epidermoid bronchial carcinoma, 1 yr of chemotherapy is significantly superior in delaying both local recurrences and distant metastases and prolonging the disease-free interval. However, BCG immunotherapy alone seems to be superior in terms of survival to no therapy, chemotherapy, and immunochemotherapy. This could be due to a better tolerance to secondary treatments given at time of recurrence. (Author abstract) (1 Ref)

12. REGIONAL IMMUNOTHERAPY HAS A DETRIMENTAL EFFECT ON THE RESPONSE TO COMBINED IRRADIATION AND CHEMOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL BRONCHOGENIC CARCINOMA.

Ruckdeschel JC, McKneally MF, Baxter DF, DeVore C, Kellar S, Killam D, Caradonna R, Sedransk N, McIlduff JB, Horton J
Dept. Medicine, Div. Oncology, Albany Medical Coll., Albany, NY, 12208
Cancer Immunol Immunother; 11(4):277-282 1981

The effect of BCG immunotherapy on the outcome of combined radiation and chemotherapy for inoperable non-small cell carcinoma of the lung (NSCC) was studied. Twenty-one patients with Stage III nonmetastatic disease confined to the thorax were treated. Eight received intrapleural saline injections; 13 received intrapleural BCG injection (10(7) Tice colony forming units). Three wk after BCG or placebo injection, combined radiation-chemotherapy was initiated. A total dose of 3,000 rads was administered in 10 increments over 2 wk. Chemotherapy was begun 7-14 days after completion of radiation therapy and consisted of cyclophosphamide [300 mg/square meter (m2)], adriamycin (20 mg/m2), and methotrexate (15 mg/m2) iv on days 1 and 8 of a 28-day cycle; procarbazine (100 mg/m2) was given po on days 2-11. Objective responses to treatment were obtained in 4/13 patients receiving BCG and 4/8 patients receiving placebo. No significant difference in response between groups was noted. Patients receiving BCG had a much shorter survival time (18 wk) than those receiving placebo (54 wk). BCG apparently has an adverse effect on combined therapy for locally advanced NSCC. (38 Refs)

13. SURGICAL ADJUVANT INTRAPLEURAL BCG TREATMENT FOR STAGE I NON-SMALL CELL LUNG CANCER.

Mountain CF, Gail MH, Lung Cancer Study Group
ECTO Operations Office, 850 Sligo Ave. Suite 601, Silver Spring, MD, 20910
J Thorac Cardiovasc Surg; 82(5):649-657 1981

The Lung Cancer Study Group has tested the efficacy of intrapleural BCG as surgical adjuvant treatment in a double-blind randomized comparison against intrapleural saline. This clinical trial included specific anatomic and pathological staging requirements and careful intrapleural follow-up monitoring. At this time, with a median follow-up of 516 days in 216 treated and 209 control patients, no evidence has yet been found that postoperative instillation of intrapleural BCG improves survival or extends the disease-free interval in patients with completely resected Stage I squamous cell carcinoma, adenocarcinoma, or large cell carcinoma of the lung. There have been 93 recurrences and 77 deaths, which are remarkably evenly distributed in both arms of the study. An unexpectedly superior survival rate for the Stage I group has been observed, and the prognostic importance of cell type, TN status, and elevations in initial white cell count and alkaline phosphatase measurement has been confirmed. (Author abstract) (21 Refs)

14. CLINICAL SIGNIFICANCE OF CONCOMITANT USE OF PSK IN 121 CASES OF PRIMARY LUNG CANCER (STAGE III AND IV) TREATED WITH COMBINATIONS OF RADIOTHERAPY AND CHEMOTHERAPY.

Ogawa Y, Kimura S, Imajo Y, Hamada F, Inomata T, Ichiyanagi A, Miyaji C, Imanaka K, Oshitani T, Takashima H, Ohbayashi K, Takada Y, Kono M
Dept. Radiology, Kobe Univ. Sch. Medicine, Kobe, Japan
Nippon Gan Chiryo Gakkai Shi; 16(4):713-723 1981

Effects of polysaccharide-Kureha (PSK) were studied in 121 patients (100 men, 21 women) with primary lung cancer that was also treated with surgery, radiotherapy, and/or chemotherapy. The PSK (3.0 g/day x 3 days, po) was administered at the same time as other initial therapies. Chemotherapeutic agents included bleomycin, mitomycin C, 5-fluorouracil, and urokinase. With respect to immunotherapy, the PSK was administered alone to 37 patients, PSK + picibanil (OK-432) were administered to 20, and no immunotherapy was administered to 64. Among the patients with Stage III lung cancer, 12-mo survival rates were significantly higher, and 50% survival period was 2x higher, in the patients given PSK + OK-432 than in those given no immunotherapy. Among the patients with Stage IV lung cancer, 50% survival periods and crude survival rates were better in patients given immunotherapy than in those not given immunotherapy, but significant differences were not observed due to severity of the disease and incomplete radiotherapy in the patients not given immunotherapy. Similar results were observed between the patients given immunotherapy and those not given immunotherapy when the tumors were analyzed according to histological types, but the differences were decreased mo 20 after treatment. (27 Refs) (In JPN)

15. LOCAL BCG-IMMUNOTHERAPY IN BLADDER CANCER PATIENTS: IMMUNOLOGICAL FOLLOW-UP STUDIES.

Seyfarth M, Hudemann B, Nizze H, Riedel H, Werner H

Dept. Immunology, Wilhelm Pieck Univ. Rostock, Leninalle 70, 2500 Rostock, E. Germany

Arch Geschwulstforsch; 52(1):63-66 1982

Local BCG therapy by intralesional injection produced some response in bladder tumors in 10/10 patients treated. Complete regression occurred in five patients. Immunological follow-up demonstrated increased leukocyte reactivity to tumor antigen in vitro (in electrophoretic mobility tests) in six patients and in vivo (in skin reactivity tests) in four patients. (9 Refs)

16. CLINICAL TRIALS OF CHEMOTHERAPY AND CHEMOIMMUNOTHERAPY IN PRIMARY MALIGNANT MELANOMA.

Jacquillat C, Banzet P, Maral J

Unite de Chimiotherapie, Institut de Recherches sur les Melanomes Malins, Lariboisiere Saint-Louis, 2 Place du Docteur Fournier, F-75475 Paris Cedex 10, France

Recent Results Cancer Res; 80:254-258 1982

We report here two randomized prospective clinical trials of adjuvant treatment in the management of primary malignant melanoma of Clark's Level III, IV or V. All patients had curative resection of the primary tumor. In the first trial, 117 patients were randomized between control (surgery alone) systemic chemotherapy and intraarterial chemotherapy. Intraarterial chemotherapy consisted of DTIC 80 mg/m 2 + 8 days prior to surgery. Systemic chemotherapy consisted of courses of vinblastine (6 mg/m2), thiotepa (6 mg/m2), rufocromycine (60 ug/m2), methotrexate (15 mg/m2) on day 1, and procarbazine (30 mg/m12) x 7 days. Courses were repeated every 2 wk x 6, then every 4 wk x 15. Twenty-two of 55 patients relapsed in the control group vs 22 of 67 in the chemotherapy group (NS). For male patients, the difference in disease-free survival was significant (p less than 0.005, log rank test), though not in women. In the second trial, 352 patients were entered from July, 1976. Men were randomized between chemotherapy and chemoimmunotherapy. Women were randomized between surgery alone and chemoimmunotherapy. Chemotherapy was identical, except for the addition of DTIC (300 mg/m2) for each course. Immunotherapy consisted of BCG every 4 wk and C parvum every wk. Immunotherapy seemed to be of no additional benefit. (Author abstract) (5 Refs)

17. TRIAL 6: RANDOMIZED STUDY OF PROLONGED CHEMOTHERAPY, IMMUNOTHERAPY, AND CHEMOIMMUNOTHERAPY AS AN ADJUVANT TO SURGERY FOR STAGE I AND II MELANOMA: A PROGRESS REPORT.

Beretta G, Rumke P, Tomin R, Mechl Z, Lejeune F, Kiss B, Kulakowski A, Cochran A, McKie R, Adamus J, Peter HH, Aubert C, Bajetta E, Bonadonna G, Cascinelli N, Morabito A, Veronesi U, Priario J, Durand J, De Marsillac J, Ikonopoisov RL, Milton GW
WHO Melanoma Group, Ospedale San Carlo, Via Venezian 1, I-20133 Milan, Italy
Recent Results Cancer Res; 80:259-263 1982

WHO clinical trial 6 studies the effect of long-term adjuvant therapy (chemotherapy, immunotherapy, and chemoimmunotherapy) after radical surgery in malignant melanoma with high risk of recurrence. The randomized study has been running for 67 mo with 845 patients. This intermediate report seems to indicate that, concerning the relapse-free period, adjuvant treatment appears superior to surgery alone. However, no significant difference in the duration of survival is evident among the four treatment groups. (Author abstract) (10 Refs)

18. GRANULOMAS IN MELANOMA PATIENTS TREATED WITH BCG IMMUNOTHERAPY.

Hatzitheofilou C, Obenchain DF, Porter DD, Morton DL
(c/o Morton) 54-140 Center Health Sciences, Univ. California, Los Angeles, CA, 90024
Cancer; 49(1):55-60 1982

Autopsy slides from 22 melanoma patients who received bacille Calmette-Guerin BCG immunotherapy and who had a postmortem examination at the UCLA Center for the Health Sciences were examined for the presence of granulomas. Granulomas were found in six patients (29%) who received BCG but not in a group of 25 melanoma patients who did not have BCG immunotherapy. A number of factors were tested for correlation with the presence of granulomas in the autopsy material. Fifty-five percent of the patients who received BCG by both intralesional and tine technique developed granulomas. No patients given BCG by the tine technique alone developed granulomas. No correlation was found between granulomas and the presence of symptoms after the administration of BCG, the duration of BCG immunotherapy, the patient's age, the number of BCG administrations, treatment with immunosuppressive agents, the length of survival after the last BCG administration, the presence of a positive PPD reaction, a positive history for granuloma-forming diseases and tests for immunocompetence. However, these results provide evidence that the route of BCG administration strongly influences the frequency of granulomas in melanoma patients who received BCG immunotherapy. (Author abstract) (25 Refs)

19. ADJUVANT IMMUNOTHERAPY OR CHEMOTHERAPY FOR MALIGNANT MELANOMA.

Fisher RI, Terry WD, Hodes RJ, Rosenberg SA, Makuch R, Gordon HG, Fisher SG
Building 10, Room 12N226, NCI, Bethesda, MD, 20205
Surg Clin North Am; 61(6):1267-1277 1981

A prospective randomized clinical trial examined whether adjuvant immunotherapy or chemotherapy prolongs the disease-free interval and ultimate survival of patients with Stage I malignant melanoma or Stage II melanoma. Following surgical treatment, 166 patients were randomized to receive either no further treatment, BCG, BCG plus neuraminidase-treated allogeneic cells, or methyl-CCNU. No significant differences in time to recurrence were observed among the four groups, although the methyl-CCNU and BCG plus vaccine curves appeared to separate from the BCG and control arms at approx 1 yr. Improvement observed in methyl-CCNU patients appeared to result from improved prognosis of Stage I patients. The methyl-CCNU patients had slightly improved disease-free survival rates compared to controls, but the small number of patients in this subgroup makes a definitive statement difficult. Toxicity related to treatment is discussed. (12 Refs)

20. LOCOREGIONAL IMMUNOTHERAPY AND CHEMOTHERAPY IN ADVANCED OVARIAN CANCER AND CYTOTOXICITY (MEETING ABSTRACT).

Ohkawa K, Ohkawa R, Shimizu Y, Mori T, Kozima Y, Ikeda S, Aoki T, Yagi Y, Hatano H

Department of Obstetrics and Gynaecology, Nippon Medical School, Tokyo, Japan

Obstetrics and Gynaecology: 8th Asian Congress, October 25-31, 1981, Melbourne, Australia. Asia and Oceania Federation of Obstetricians and Gynaecologists 352 pp., 1981.

Cancerimmunotherapy is the enhancing of the function of the lymphatic system. The suppressed function of the lymphatic system of cancer patients further loses its function due to surgical intervention, the use of anti-cancer agents, and radiotherapy. We tried to enhance the function of the lymphatic system after application of anti-cancer agents. For immunotherapy we used semi-synthesized acid polysaccharides, BCG and OK 432 and so on. From Monday to Thursday immunotherapy of acid polysaccharides intraabdominally was performed, and BCG was inoculated in the skin and OK 432 was used intraabdominally or intracutaneously. For chemotherapy we used polychemotherapy of 5 anti-cancer agents intraabdominally through a polyethylene tube every Friday. (The 5 anti-cancer agents are as follows; adriamycin, 5 fluorouracil, endoxan, bleomycin and mitomycin). A skin test for delayed hypersensitivity was performed. The complement activity was measured and cytotoxicity was measured by means of Hellstrom's method. Out of 75 cases of advanced ovarian cancer treated from 1970 to 1977, 3 yr survival is 40% and out of 60 cases, 5 yr survival is 40%. Enhancing of activity of complement after immunotherapy is necessary for good prognosis. Enhancing of the skin test and of cytotoxicity are also necessary for good prognosis. It is concluded that locoregional immunotherapy and chemotherapy are effective. (no Refs)

21. 17. ADJUVANT INTERFERON TREATMENT OF HUMAN OSTEOSARCOMA.

Strander H, Aparisi T, Blomgren H, Bromstrom LA, Cantell K, Einhorn S, Ingimarsson S, Nilsonne U, Soderberg G

Karolinska Hosp., S-104 01 Stockholm, Sweden

Recent Results Cancer Res; 80:103-107 1982

This paper updates the results of the clinical trial to examine the efficacy of exogenous leukocyte interferon therapy as adjuvant treatment for osteosarcoma. So far the incidence of metastases is lower and the survival rate is better for the interferon-treated group than for the concurrent control group. The number of treated patients is too small at present to allow proper statistical calculations to be made. (Author abstract) (19 Refs)

22. A CONTROLLED CLINICAL AND IMMUNOLOGICAL EVALUATION OF IMMUNOTHERAPY WITH BACILLUS CALMETTE-GUERIN IN PATIENTS WITH METASTATIC CANCER.

O'Connell MJ, Ritts RE, Moertel CG, O'Fallon JR, Rubin J, Frytak S, Schutt AJ

Dept. Oncology, Mayo Clinic, Rochester, MN, 55901
Cancer Clin Trials; 4(4):439-449 1981

One hundred thirty adult patients with metastatic solid tumors were studied to evaluate the therapeutic results, toxicity, and immunological effects of three BCG preparations given intradermally by the multiple puncture time technique on either a monthly or weekly schedule: Tice lyophilized BCG, Pasteur lyophilized BCG, and Pasteur fresh-frozen BCG. Patients were randomly assigned in a double-blind manner to receive one of the BCG preparations or saline placebo administered in an identical manner. A battery of immunological tests were performed pretreatment and serially during the investigation. None of the 82 patients with measurable indicator lesions experienced an objective tumor response, nor were there any differences in survival among patients receiving any of the BCG preparations compared to placebo. Toxicity consisted of mild to moderate local cutaneous reactions and liver function abnormalities in BCG-treated patients with no significant differences between BCG preparations. Improvements in each of the assays of immune function performed occurred with roughly equal frequency among patients receiving BCG or placebo. It was not possible to demonstrate any significant clinical or immunological benefit from BCG administration in this patient population with the methodology employed. (Author abstract) (25 Refs)

23. PHASE III STUDY OF LENTINAN.

Furue H, Itoh I, Kimura T, Kondo T, Hattori T, Ogawa N, Taguchi T
Second Dept. Internal Medicine, Teikyo Univ., Sch. Medicine, Itabashi-ku, Tokyo 173, Japan
Gan To Kagaku Ryoho; 8(6):944-966 1981

To evaluate the clinical efficacy of lentinan, an immunopotentiating agent and purified polysaccharide (beta[1 leads to 3]glucan) extracted from Lentinus edodes (an edible Japanese mushroom), a randomized control study (envelop method) was performed on patients with advanced or recurrent gastric or colorectal cancer in 64 major institutions, comparing 'combination therapy with lentinan and chemotherapeutic agent' with 'chemotherapy alone' as a control. As control chemotherapy, the combined administration of mitomycin C and 5-fluorouracil (MF) or the single administration of tegafur (FT) was selected. Five hundred and twenty-three patients were entered in the study. There were 239 patients in the control chemotherapeutic group (control group) and 284 patients in the group given combination therapy with lentinan and chemotherapeutic agent (treated group). Three hundred and seventy-five of the 523 patients were eligible, and there were 168 patients in the control group and 207 patients in the treated group. The clinical efficacy of lentinan was evaluated by its antitumor effect, prolongation of life and improvement in host immune response. Compared with chemotherapy alone, statistically significantly higher incidence of antitumor effect and prolongation of life were observed with lentinan treatment. By both purified protein derivatives skin tests and increase in peripheral blood lymphocytes counts, a greater improvement in host immune response was observed with lentinan treatment, and improvement in the host immune response coincided with prolongation of life. In all of the 284 patients in the treated group, side effects, which were observed in 16 patients, seemed to be caused by combination therapy with lentinan and MF or FT. The incidence was similar to that in the Phase I and II studies, and all side effects were transitional and not very serious. These results suggest that lentinan would be of use for patients with gastrointestinal cancer as an immunopotentiator in combination with chemotherapeutic agents. (27 Refs) (In JPN)

24. CLINICAL EVALUATION OF IMMUNOCHEMOTHERAPY WITH STREPTOCOCCAL PREPARATION 'OK-432' ON INOPERABLE ADVANCED CANCERS.

Nio Y, Nitta N, Tanaka A, Ichikawa T, Henmi K
Dept. Surgery, Ako Municipal Hosp., Nakasu, Kariya, Ako, Hyogo Prefecture 678-02, Japan
Nippon Geka Hokan; 50(5):704-710 1981

Results of treating 54 patients with OK-432 (picibanil) in combination with antineoplastic chemotherapy for advanced, inoperable cancers were compared with those in 70 patients treated with chemotherapy without OK-432 and those in 61 patients who were not treated with chemotherapy or OK-432. The patients in the combination group had gastric (17 cases), colorectal (4), liver (7), pancreas (3), gall bladder (4), or lung (16) cancers, or cancerous peritonitis (3). The patients in the chemotherapy group had gastric (31), colorectal (3), liver (7), gall bladder (2), or lung (16) cancers. Patients were administered 0.2-0.5 IU of the OK-432 every day or qod initially, and were given 1-5 IU as maintanence doses. According to Karnofsky's criteria, effective treatment (I-A, I-B, or I-C) ratings were obtained in 4/63 evaluable patients in the chemotherapy group and in 11/52 evaluable patients in the combination group. Mean survival times for the non-chemotherapy group patients, the chemotherapy group patients, and the combination group patients were 2.2 mo, 4.2 mo, and 5.9 mo, respectively, and the 1-yr survival rates were 0%, 6.0%, and 18.0%, respectively. Improved clinical results and survival rates were thought to be possible with immunochemotherapy based on OK-432. (17 Refs) (In JPN)

25. PHASE I TRIAL WITH THE IMMUNOTHERAPEUTIC AGENT OK-432 (MEETING ABSTRACT).

Micksche M, Kokoschka EM, Uchida A
Department of Dermatology, University of Vienna, Vienna, Austria
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

The streptococcal preparation OK-432 has been intensively investigated for its immunomodulating and therapeutic efficacy in cancer patients mainly in Japan. In a Phase I trial, including 35 patients with malignant melanoma for possible side effects of this preparation when given im, iv, id, it, intrapleural or ip. Iv route and intracavitary application always led to rise of body temperature, being the only one side effect observed. Clinical outcome was evaluable in 22 patients with advanced malignant melanoma having received several doses of OK-432 by a variety of routes for a longer period of time. It may be considered favorable in 14 of them, including one complete remission of pulmonary metastases maintained for more than 4 mo by continuous therapy. Immunopharmacological studies showed that iv and id injection of one single dose (1 KE) of OK-432 is significantly enhancing natural killer cell activity with a max on day 3 when measured in a 4-hr chromium-51 release assay against K562 targets. Intrapleural application, furthermore, led to a reduction of suppressor cells against natural killer cells, which we have demonstrated to be present in malignant pleural effusions. Furthermore, we were able to demonstrate that in vitro incubation patients's lymphocytes with OK-432 significantly enhanced lymphocyte cytotoxicity in a dose-dependent manner comparable to that of Hu IFN. According to our studies, OK-432 seems to be a potent immunomodulator which also shows some clinical efficacy even when given to patients with advanced malignant disease. (1 Ref)

SYNTHETIC IMMUNOTHERAPEUTIC AGENTS

26. IN VIVO ACTIVATION OF MACROPHAGES BY CORYNEBACTERIUM PARVUM, PYRAN COPOLYMER AND GLUCAN.

Barlin E, Leser HG, Deimann W, Resch K, Gemsa D
(c/o Gemsa) Inst. Immunology, Univ. Heidelberg, Im Neuheimer Feld 305, D-6900 Heidelberg, W. Germany
Int Arch Allergy Appl Immunol; 66(Suppl1):180-182 1981

Three immunopotentiators (IMP) were used to examine whether a high release of prostaglandin E (PGE) from macrophages is a general attribute of activated macrophages or whether it is dissociable from typical functions such as tumor cytotoxicity. Various times after ip injection of C57Bl/6 mice with Corynebacterium parvum (CP; 0.3 mg), pyran copolymer (0.5 mg) or glucan (2 mg), peritoneal macrophages were prepared. PGE was determined by radioimmunoassay. As determined by a tumor cytotoxicity test, all three IMP induced activated macrophages. In spleen, the IMP induced nearly identical increases of macrophages (5 to 20-30%). While all the IMP resulted in a two- to three-fold enhancement of PGE release from spleen cells 1 day after their injection, PGE production after CP reached high levels after 4-16 days. The proliferative response of spleen lymphocytes to Concanavalin A (Con A) stimulation (2.5 ug/ml) was also performed. One day after injection, Con A response of lymphocytes was elevated with all three IMP; however, on following days the only change relative to lymphocytes from unstimulated mice, was a long-lasting suppression due to CP. When PGE synthesis in spleen cell cultures was inhibited by indomethacin, lymphocyte response was competely restored at day 4 after CP injection. Early lymphocyte response (less than 8 days) could be restored by selectively removing strongly-adherent, PGE-producing macrophages by passage over rayon and wool. Such manipulation between days 8 and 16 after CP injection did not alter lymphocyte response. (3 Refs)

INTERFERON

27. EFFECT OF LONG-TERM ADMINISTRATION OF INTERFERON ON NK CELL ACTIVITY IN MICE AND IN PATIENTS (MEETING ABSTRACT).

Goutner A, Bruley-Rosette M, Florentin I, Misset JL, Ribaud P, Mathe G
Hopital Paul-Brousse, 94804 Villejuif, France
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

In mice, a single injection of mouse interferon induces an increase in NK activity of spleen cells measured on Yac target cells. Long-term administration of 10(4) units of interferon per wk results in a decrease of NK cell activity in young mice with initially normal cytotoxic ability and an increase in old mice, which have a depressed level of cytotoxicity due to aging. Thus the effect of long-term administration of exogenous interferon is dependent on the initial level of NK cell activity, suggesting complex regulatory mechanisms of the function. Sixteen myeloma patients were submitted to a phase II trial of fibroblastic interferon (provided by Roswell Park Memorial Institute) and their NK cell activity in the peripheral blood mononuclear cells was sequentially evaluated on K 562 target cells. Unexpected results were observed compared to those registered in chronic leukemia patients. Before the treatment, NK cell activity was significantly elevated compared to normal controls in 8/16 patients, normal in 2 patients and depressed in 6.6 million units of fibroblastic interferon were administered per wk from 1 to 10 wk. Four of 8 patients with initially elevated NK activity experienced a decrease of this activity. Elevation was observed in patients with low NK cell activity. (no Refs)

28. EFFECT OF FIBROBLAST - INTERFERON (IF-BETA) ON COLONY TUMOR GROWTH OF MISCELLANEOUS CARCINOMAS (MEETING ABSTRACT).

Schlag P, Schreml W, Herfarth C
Department of Surgery, University of Ulm, Steinhoevelstrasse 9, 7900 Ulm, W. Germany
Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussels, Belgium European Organization for Research on Treatment of Cancer; :A99 1981

The effect of fibroblast interferon on colony tumor growth of 42 miscellaneous carcinoma (15 gastric-, 11 breast-, 8 colon-, 3 bronchial carcinomas) and two malignant melanomas were assayed. Of the 44 evaluable experiments only 4 tumor specimens showed at least a 30% inhibition of colony formation in the presence of interferon at concentrations of 1000 units/ml or less. In these cases, a dose response relationship was obvious. In the other 40 tumors, colony tumor growth was not significantly influenced by fibroblast interferon. Since differences were observed in the activity of interferon in lymphnode-metastases in comparison to the simultaneously tested primary tumor, it is suggested that presence of immunocompetent cells is essential for the inhibition of colony tumor growth by interferon. (no Refs)

29. IN VITRO AND IN VIVO NK CELL MODULATION BY BIOLOGICAL RESPONSE MODIFIERS (BRM) IN CANCER PATIENTS (MEETING ABSTRACT).

Serrou B, Cupissol D, Favier F, Rosenfeld C
Department of Chemo-Immunotherapy, Hopital St. Eloi, BP 5054, 34033 Montpellier Cedex, France
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Many recent data suggest that non immunodepressed patients respond better to chemotherapy than immunodepressed patients. This fact, closely related to the immune imbalance of the cancer patient, of itself justifies the recent interest in BRM. In vitro and in vivo in immunodepressed solid tumor bearing patients, we evaluated the immunorestorative potential of 5 BRM: human fibroblast interferon (HFIF) injected IV, Bestatin purified from Streptomyces olivoreticuli, NPT 95 392 which is a new Isoprinosine derivative, RO 95132 a retinoic acid derivative. These BRM were used for 3 wk and all parameters were evaluated before and after treatment. At the doses used, no BRM presented major side effects (hepatic or renal dysfunction, blood pressure, cardiac function, hematological modification). Natural killer (NK) activity showed significant changes for all drugs, although NK activity significantly increased only after HFIF and Bestatin. These results underline the increasing attention being given to these BRM which are now just entering phase 3 studies as adjuvant therapy (Bestatin), or phase 2 studies either alone (HFIF) or associated with chemotherapy. (no Refs)

30. HIGH AFFINITY BINDING OF 125I-LABELED MOUSE INTERFERON TO A SPECIFIC CELL SURFACE RECEPTOR. II. ANALYSIS OF BINDING PROPERTIES.

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Virology; 115(2):249-261 1981

Direct ligand-binding studies with highly purified 125I-labeled virus-induced mouse interferon on mouse lymphoma L1210 cells revealed a direct correlation of specific high-affinity binding with the biologic response to interferon. Neutralization of the antiviral effect by anti-interferon gamma globulin occurred at the same antibody concentration as the inhibition of specific binding. These results suggest that specific high-affinity binding of 125I-interferon occurred at a biologically functional interferon receptor. Competitive inhibition experiments using 125I- and 127I-labeled interferon provided strong evidence that the fraction of 125I-interferon inactivated upon labeling did not bind specifically. Scatchard analysis of the binding data yielded linear plots and thus suggested that interferon binds to homogeneous noncooperative receptor sites. In contrast to a characteristic property of several peptide hormone systems, binding of 125I-interferon to its specific receptor did not induce subsequent ligand degradation. At 37 C bound interferon was rapidly released in a biologically active form without evidence for molecular degradation. The expression of interferon receptors was not modified by treatment with interferon. Trypsin treatment of target cells and inhibition of protein synthesis abolished the specific binding of 125I -interferon. three major mol wt species of Newcastle disease virus-induced mouse C 243 cell interferon were isolated separately and identified as mouse alpha and beta interferons. These interferons were shown to inhibit competitively the specific binding of the highly purified labeled starting material which contained all three size species, thus providing evidence for a common receptor site for mouse alpha and beta interferon. (Author abstract) (24 Refs)

31. RAPID INCREASE IN GUANOSINE 3',5'-CYCLIC-MONOPHOSPHATE IN INTERFERON-TREATED MOUSE LEUKEMIA L1210 CELLS: RELATIONSHIP TO THE DEVELOPMENT OF THE ANTIVIRAL STATE AND INHIBITION OF CELL MULTIPLICATION.

Tovey MG, Rochette-Egly C
Institut de Recherches Scientifigues sur le Cancer, Villejuif, France
Virology; 115(2):272-281 1981

Treatment of mouse leukemia L1210 cells with electrophoretically pure mouse interferon caused a rapid (1 to 5 min) and transitory (duration 5 to 10 min) increase in the intracellular concentration of guanosine 3',5'-cyclic monophosphate (cyclic GMP). No significant increase in the intracellular concentration of adenosine 3',5'-cyclic monophosphate (cyclic AMP) was observed until 2 to 3 hr after the addition of interferon. Electrophoretically pure mouse interferon caused a dose-dependent increase in the intracellular concentration of cyclic GMP at concentrations ranging from 1.0 to 10(4) units/ml.

The interferon-induced increase in cyclic GMP was abrogated by specific antibody to mouse interferon. Furthermore, interferon had no effect on the intracellular concentration of cyclic GMP in a line of L1210 cells resistant to the action of interferon. The interferon-induced increase in cyclic GMP was calcium dependent and was inhibited by indomethacin and aspirin at concentrations of 10(-7) to 10(-5) M. Depletion of intracellular calcium prior to the addition to interferon abrogated the interferon-induced increase in cyclic GMP without preventing either the development of the antiviral state or the inhibition of cell multiplication in interferon-treated L1210 cells. These results suggest that cyclic GMP may not mediate these two biologic effects of interferon but may rather reflect rapid changes in interferon-treated cells. (Author abstract) (29 Refs)

32. IN VITRO PHASE II STUDY WITH INTERFERON ALPHA2 (E. COLI) (MEETING ABSTRACT).

Hofmann V, Martz G, Weissmann C

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Third NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 15-17, 1981, Brussels, Belgium European Organization for Research on Treatment of Cancer; :A28 1981

Using clonogenic assays for solid tumors and myelogenous leukemias we have examined the activity of highly purified cloned interferon alpha 2 (IFN). Eleven solid tumors were grown in semi solid agar using the Salmon-Hamburger technique. Triplicates of control and IFN-treated plates were regularly checked for growth using an inverted microscope and counted after 7-28 d. The tumor cell suspensions were incubated at 37C for 1 hr with IFN at dose levels ranging from 10 to 10,000 U/ml and then plated. Colony formation was reduced to 17% in 1 metastatic adenocarcinoma of unknown origin. Survival curves varied between 50 and 150% in 7/11 tumors (2 breast, 1 lung, 2 melanoma, 1 bladder, 1 ovary). Colony formation was increased to levels between 230 and 460% at 100-1,000 U/ml in 3/11 tumors (1 breast, 1 lung, 1 ovary). Eight acute myelogenous leukemias were tested in agar-methylcellulose using phytohemagglutinin-WBC conditioned medium. IFN was incubated with the cell suspensions as described above at dose levels ranging between 100 and 10,000 U/ml. At the 1,000 U/ml level 3 leukemias demonstrated colony survival of 42, 38, and 8%. At the 10,000 U/ml level no further suppression was observed in the 2 first cases (1 M5 and 1 M2), while colony survival in the third (M2) was reduced to 3%. At this same dose level 2 other leukemias (1 M0 and 1 M5) which showed no significant suppression at lower IFN levels, were reduced to 1%. Three leukemias (2 M4 and 1 M2) were not markedly affected by IFN. In 2 pts resistant to chemotherapy identical dose-response curves to IFN were observed when the experiments were repeated after 9 and 13 wk. (1 Ref)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

33. EXPERIMENTAL AND CLINICAL STUDIES OF IMMUNOLOGICAL ACTIVITY OF MONOCYTES IN TUMOR-BEARING HOSTS. I. KINETICS OF PERITONEAL MACROPHAGE FUNCTIONS IN TUMOR-BEARING MICE.

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Dept. Surgery, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi, Hiroshima 734, Japan

Hiroshima Daigaku Igaku Zasshi; 29(3):491-502 1981

The immunological reactivity of nonactivated and Corynebacterium parvum (C parvum)-activated peritoneal macrophages in tumor-bearing mice was investigated in relation to several macrophage functions - chemotaxis, phagocytosis, cytostasis, cytolysis and serum lysozyme activity. Peritoneal exudate cells (PEC) decreased from Day 14 after tumor inoculation and more significantly at day 28. The number of PEC from tumor-bearing mice treated with C parvum increased, but, in the late stage, less than in normal C parvum-treated mice. The response to WBC-derived chemotactic factor was significantly depressed in the early stage of the tumor-bearing mice and did not recover until the late stage. It was increased by injection of C parvum, but less after Day 7 than that of C parvum-treated normal mice. Phagocytosis of latex beads increased significantly within 10 days after tumor inoculation, then progressively decreased to normal and remained normal until death. It was increased by C parvum as much as that from C parvum-treated normal mice. Cytostatic activity of tumor-bearing mice increased in the early stage, then decreased. It seemed to be related to immunocompetence and prognosis of tumor-bearing mice. C parvum increased the even activity in the late stage. Cytolytic activity of tumor-bearing mice was initially absent, but became apparent when the tumor grew, reached a max on Day 10 and decreased in the late stage. It was enhanced by C parvum, but less in tumor-bearing mice than in normal mice. Serum lysozyme activity, a possible marker of macrophage function, showed a small increase in tumor-bearing mice but no further progression. It either increased or decreased after treatment with C parvum. (Author abstract) (39 Refs) (In JPN)

34. EXPERIMENTAL AND CLINICAL STUDIES OF IMMUNOLOGICAL ACTIVITY OF MONOCYTES IN TUMOR-BEARING HOSTS. II. CYTOSTATIC ACTIVITY OF TUMOR-BEARING MOUSE PERITONEAL MACROPHAGES FRACTIONATED BY VELOCITY SEDIMENTATION.

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Dept. Surgery, Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Kasumi, Hiroshima 734, Japan

Hiroshima Daigaku Igaku Zasshi; 29(3):503-517 1981

The cytostatic activity of nonactivated and Corynebacterium parvum (C parvum) activated peritoneal macrophages from tumor-bearing mice was reported previously. In the present study, macrophages were fractionated by velocity sedimentation and analyzed to investigate the immunocompetence of tumor-bearing mice. Cytostatic activity of macrophages from normal mice was absent at low effector to tumor (E/T) ratios but present at high E/T ratios. On the other hand, macrophages from tumor-bearing mice showed some cytostatic activity at low E/T ratios. The difference in cytostatic activity between normal and tumor-bearing mice seemed partially dependent on the E/T ratio. It was suggested that cytostatic activity of unfractionated macrophages be tested at many E/T ratios. According to cell size by velocity sedimentation, the sedimentation profile of peritoneal exudate cells (PEC) of normal mice showed a bimodal distribution. In contrast, that of C parvum-treated normal mice showed a unimodal distribution. The sedimentation profile of the PEC from tumor-bearing mice was unimodal in the early stage and bimodal in the late stage. That of PEC from C parvum-treated tumor-bearing mice showed no clear unimodal distribution. Cytostatic activity of macrophages from normal mice increased with cell size and was max with the largest macrophages. On the other hand, cytostatic activity of fractions containing small and medium-sized macrophages from tumor-bearing mice was high in the early stage and significantly lower in the late stage. However, cytostatic activity of fractions containing large macrophages from tumor-bearing mice was as high as that from normal mice. These results suggest that the cytostatic activity of fractionated macrophages could be a good indicator for analyzing macrophage-mediated host resistance to tumors. (Author abstract) (20 Refs) (In JPN)

35. COMBINED CHEMOTHERAPY-RADIOTHERAPY ON SPLEEN HYPERTROPHY AFTER C. PARVUM: COMBINED TREATMENT WITH 5-FU, CYCLOPHOSPHAMIDE AND RADIATION.

Maruyama Y, Grider C, Williams A
Radiation Medicine, Univ. Kentucky Medical Center, Lexington, KY, 40536
Int J Radiat Biol; 40(5):475-482 1981

C parvum (CP) acts as a powerful stimulant for cell proliferation in the normal spleen. CP, in combination with radiation or cytotoxic chemotherapeutic agents, interfered with their effect to a lesser or greater degree depending upon the sequence in which CP and the cytotoxic therapy was applied. In these experiments, cyclophosphamide (CY), 5-fluorouracil and radiation were studied singly or in combination during the resting or after CP-stimulation, and the effects of the different combinations of chemotherapy and radiotherapy determined. Interestingly, CY acted both as a stimulant and suppressant for the spleen growth response when combined with CP. This may contribute to the reported effectiveness of the combination used for therapy in certain antigenic tumor systems. Radiation had a strongly suppressive effect on spleen response to CP in any sequence studied. (Author abstract) (28 Refs)

36. DESTRUCTION OF TUMOR CELLS BY MACROPHAGE PRECURSORS IN MOUSE AND MAN.

Lohmann-Matthes ML, Zahringer M
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Blut; 42(5):283-295 1981

Macrophage precursors exhibiting killer cell (K-cell) and natural killer cell (NK-cell) activity were detected in vivo in mice and humans. Peritoneal exudate was induced in C57/BL10 mice by ip injection of 100 ug Corynebacterium parvum. The exudate showed K-cell and NK-cell activity against Yac-1 and DBA/2 P815X tumor cells. Separation by column adherence produced a population of nonadherent cells, consisting of small lymphocytes and middle-sized, promonocyte-like cells (PML), which had K-cell and NK-cell activity. The PML lacked nonspecific esterase (a marker for mature macrophages), but when cultured produced mature macrophages after 3 days, indicating that the cultured cells were macrophage precursors. Similar cells were isolated from spleens of nu/nu mice and from human peripheral blood. The activity of these cells was absorbed by allogeneic antimacrophage serum Mph 1.2 with rabbit complement. The cells were nonadherent and nonphagocytic. Results indicate that macrophage precursor cells, as well as mature macrophages, are released from bone marrow into peripheral circulation in mice and humans, and that these precursor cells have cytotoxic effects on tumor cells. (24 Refs) (In GER)

37. IMMUNOPOTENTIATING ACTION OF STREPTOCOCCAL PREPARATION OK-432 AND PROTEIN-BOUND POLYSACCHARIDE PS-K ON DEPRESSED STATE OF CELL-MEDIATED AND HUMORAL IMMUNITIES OF FRIEND LEUKEMIA VIRUS INFECTED MICE.

Kiyohashi A
Dept. Internal Medicine, Sch. Medicine, Kitasato Univ., Japan
Nippon Gan Chiryo Gakkai Shi; 16(4):641-646 1981

The effects of OK-432, a penicillin-treated Group A hemolytic streptococci, and PS-K, a protein-bound polysaccharide, on the immune response of male ICR and ddY mice infected with Friend leukemia virus (FLV) were examined. FLV-infected mice were injected iv with either 0.5 KE (1 KE = 0.1 mg lyophilized streptococci) OK-432 or 30 mg/kg PS-K daily for 3 consecutive days, from 5 days before and from 3 days after FLV inoculation. Lymph node cells of mice treated with both FLV and OK-432 responded well to ovalbumin (OA) and purified protein tuberculin derivative in macrophage migration inhibition tests conducted 21-31 days after immunization with OA. Mice treated wtih FLV and PS-K showed no response. Both response of hemolytic plaque forming cells to sheep RBC (anti-SRBC PFC) and serum antibody production were not detected in the FLV-infected mice, whether injected with OK-432 or PS-K. The anti-SRBC PFC response and antibody production in OK-432-treated mice were slightly greater than those in the other FLV-infected groups, but the differences were not significant. The results suggested that OK-432 has an immunopotentiating activity on the depressed state of cell-mediated immunity, while PS-K does not. Neither PS-K nor OK-432 enhanced humoral immunity in FLV-infected mice. (13 Refs)

CYTOKINE THERAPY

38. IN VITRO AND IN VIVO INDUCTION OF CYTOTOXIC LYMPHOCYTES BY INTERLEUKIN 2 (IL2) (MEETING ABSTRACT).

Hersey P, Binden C, Edwards A, Murray E, Milton GW
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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

IL2 is a lymphokine released from helper t cells which is necessary for the generation of cytotoxic L lymphocytes. The purpose of this study was to examine whether stimulation of lymphocytes in vitro and in vivo with IL2 would induce cytotoxic T cells against autologous melanoma cells. IL2 was isolated from 24 hr phytohemagglutinin (PHA) stimulated lymphocyte supernatants by membrane chromatography. Incubation of lymphocytes from melanoma patients in IL2 (2u/ml) for 6 days resulted in generation of cytotoxic cells against autologous and allogeneic melanoma and non-melanoma target cells. Cold target inhibition studies suggested the latter was due to killing by natural killer or activated T cells. Killing of autologous melanoma cells appeared to be due to T cells specific for these cells. In vivo injection of IL2 containing supernatants in 2 patients (no PHA) resulted in a number of changes in the immune system but at 5 to 7 days cytotoxic lymphocytes against allogeneic and autologous melanoma cells were detected which lasted for several days. Data on IL2 clearance rates and other immunological data will be presented. These results suggest that IL2 may be a relatively non-toxic but effective agent for the induction of cytotoxic T cells against melanoma and may have an important role in immunotherapy. (no Refs)

39. BIOCHEMICAL AND BIOLOGIC CHARACTERIZATION OF LYMPHOCYTE REGULATORY MOLECULES: VIII. PURIFICATION OF INTERLEUKIN 2 FROM A HUMAN T CELL LEUKEMIA.

Frank MB, Watson J, Mochizuki D, Gillis S
Dept. Microbiology, Univ. California, Irvine, CA, 92717
J Immunol; 127(6):2361-2365 1981

The ability of interleukin 2 (IL 2) to stimulate and maintain growth in IL 2-dependent cell lines distinguishes this substance from interleukin 1 and other T cell lymphokines. Jurkat-FHCRC, a human T cell leukemia cell line, has been shown to produce relatively high quantities of IL 2 after stimulation with the T cell mitogens phytohemagglutinin or concanavalin A. In this paper we describe techniques used to isolate human IL 2 from Jurkat supernatants and the biochemical properties of the resulting material. IL 2 produced by this cell line is eluted from a DEAE-Sephacel ion-exchange column with 0.05 M NaCl and has a mol wt determined by AcA54 gel chromatography in the range of 9,000 to 18,000. Isoelectric focusing yields active material with a pI value of 7.75. Elution of IL 2 from a SDS-polyacrylamide gel shows it to have a mol wt of approx 13,500. This material is capable of stimulating mouse as well as human IL 2-dependent cell lines. (Author abstract) (25 Refs)

40. TRANSLATION OF LYMPHOCYTE MRNA INTO BIOLOGICALLY-ACTIVE INTERLEUKIN 2 IN OOCYTES.

Bleackley RC, Caplan B, Havele C, Ritzel G, Mosmann TR, Farrar JJ, Paetkau V
(c/o Paetkau) Dept. Biochemistry, Univ. Alberta, Edmonton, Alberta T6G 2H7, Canada
J Immunol; 127(6):2432-2435 1981

A variant line of murine T lymphoma EL4 produces high levels of the lymphokine Interleukin 2 (IL 2) when it is stimulated with phorbol myristate acetate. We have extracted poly A+ RNA from the stimulated cells and injected it into Xenopus laevis oocytes. The injected oocytes synthesize a material with biological and biochemical properties of murine IL 2. Namely, it stimulates the continued growth factor of a cloned, cytotoxic T-cell line (the T-cell growth factor assay) and it chromatographs on a gel filtration column (G-100) with IL 2 produced by the stimulated EL4 line. The RNA responsible for the biologic activity sediments with markers of 11 to 12S in a sucrose gradient. The IL 2 produced by injected oocytes from a given preparation of mRNA is about 1% of the amount produced by the EL4 cells stimulated originally with phorbol myristate acetate. When RNA is extracted and purified from unstimulated EL4 cells it does not induced IL 2 production in oocytes. We conclude that IL 2 is essentially protein in nature, that the protein is coded for by poly A+ mRNA, and that the amount of this mRNA increases significantly after stimulation of the variant EL4 cells with the inducer phorbol myristate acetate. (Author abstract) (19 Refs)

41. CHARACTERISTICS OF AN ANTIGEN-SPECIFIC HELPER FACTOR THAT ENHANCES THE IN VITRO GENERATION OF CYTOTOXIC CELLS DIRECTED AGAINST A SYNGENEIC TUMOR.

Kilburn DG, Talbot FO, Levy JG
Dept. Microbiology, Univ. British Columbia, Vancouver, B. C., V6T 1W5, Canada
J Immunol; 127(6):2465-2469 1981

An antigen-specific helper factor (Hf) that enhances the in vitro generation of tumor-specific cytotoxic T cells (CL) has been isolated from the spleens of DBA/2 mice bearing the syngeneic mastocytoma, P815. This factor enhances the CL response to P815 but not to L1210 (a syngeneic T cell leukemia in DBA/2 mice), B10 minor antigens, or DBA/2 alloantigens. The factor binds specifically to P815 membrane immunoadsorbent columns and can be eluted with 2 M NaCl. P815 Hf did not resemble the lymphokine IL 2 because it did not enhance the proliferative or CL response of thymocytes nor would it support the growth of an IL 2-requiring line of T cells. This factor acted optimally if added late in the culture period in contrast to IL 2, which was more effective if added early. In limiting dilution experiments P815 Hf enhanced the level of CL activity generated but not the number of precursors triggered. IL 2 markedly amplified both of these parameters. (Author abstract) (27 Refs)

42. T CELL RECOGNITION OF MOLONEY LEUKEMIA VIRUS PROTEINS: III. T CELL PROLIFERATIVE RESPONSES AGAINST GP70 ARE ASSOCIATED WITH THE PRODUCTION OF A LYMPHOKINE INDUCING 20 ALPHA-HYDROXYSTEROID DEHYDROGENASE IN SPLENIC LYMPHOCYTES.

Ihle JN, Lee JC, Rebar L
Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
J Immunol; 127(6):2565-2570 1981

One of the characteristic cellular immune responses associated with the regression of Moloney leukemia/sarcoma virus-induced tumors is a T cell proliferative response against the major viral envelope glycoprotein, gp70. The results described here demonstrate that associated with this proliferative response is the production of a lymphokine, Interleukin 3 (IL-3). The production of IL-3 was immunologically specific and showed the same specificity as that observed in blastogenic responses. IL-3 production was dependent upon an antigen-specific Thy-1.2+, Lyt-1+, 2-lymphocyte subpopulation but did not require the presence of an Ia+ or an adherent accessory cell. The results also suggested that IL-3 may constitute one of the blastogenic factors previously shown to be involved in the proliferative response to gp70. In particular purified IL-3 was found to induce proliferation of both normal and immune nylon wool purified splenic lymphocytes. The phenotype of the responding lymphocyte subpopulation was Thy-1.2-, Lyt-1-, 2-, Ig-, and Ia-. Maximal IL-3 production occurred approximately 48 hr after the addition of antigen and its production was significantly blocked by mitomycin C. These characteristics were unlike those for the general production of blastogenic factor activity suggesting that IL-3 is responsible for only a minor component of the proliferative response. (Author abstract) (19 Refs)

ACTIVE SPECIFIC IMMUNIZATION

43. LIPOSOME-MEDIATED IN VITRO INDUCTION OF PRIMARY CELL-MEDIATED IMMUNITY TO HUMAN CANCERS (MEETING ABSTRACT).

Tom BH, Sengupta J, Liu JS, Raphael L
University of Texas Medical School, Houston, TX, 77030
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

The availability of an in vitro method for generating immune responses to human cancers is highly desirable. Indeed many investigators the past decade have reported studies describing in vitro induction of immunity. However, the difficulties in using whole tumor cells as immunogens have thwarted efforts to characterize and exploit the methodologies. Subsequent immunization efforts with cell-free tumor systems have been equally unimpressive. Most recently, liposomes have been demonstrated to be useful adjuvants, as well as convenient antigen carriers, eg, eliciting immunity not produced by free antigen. Although primary immunity to lymphoid tumors has been reported, no laboratory has yet described the in vitro induction of a primary cell-mediated immune response to nonlymphoid human tumors, such as colon or breast, with cell-free antigens. The present report provides data demonstrating the generation of an in vitro xenoimmune response to human colon cancer. The cell-mediated immunity to colon cancer was induced with liposomes in murine splenocytes and requires T-lymphocyte function. Furthermore, optimal results were produced when the tumor antigen was exposed on the liposome surface. Utilizing the same system, colon tumor immunity has been generated in human peripheral blood lymphocytes. However, unlike the murine system, only blastogenic, and not cytotoxic cells were produced. Nevertheless, exploitation of this in vitro approach should prove useful in dissecting the molecular factors necessary in providing immunogenic stimuli in human tumor immunity. (no Refs)

SEROTHERAPY AND RELATED APPROACHES

44. APPLICATION OF MONOCLONAL ANTIBODIES TO THE STUDY OF HUMAN CANCER (MEETING ABSTRACT).

Steplewski Z
The Wistar Institute, 36th and Spruce, Philadelphia, PA
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Monoclonal antibodies are used by our group to define antigens of human solid tumors. Most of the antigens detected on the surface of human melanomas are glycoproteins. In the case of gastrointestinal (GI) tumors however, murine monoclonal antibodies are detected in the majority of cases against glycolipid moieties. Several of these antibodies stain strongly in immunoperoxidase procedure (Bouin's fixed, paraffin-embedded specimens). The distribution of a monosialoganglioside antigen in tissues was presently confirmed in immunoperoxidase assays. The antigen was present in 50% of colon carcinomas and in all carcinomas of pancreas (7/7) and stomach (4/4) tested. Breast (0/12) and lung (0/5) tumors were negative. Interestingly, antigen was also detected in 11/15 adenomatous polyps, including 6/8 villous adenomas. This antigen was also detected in pancreatic hepatic ducts, bronchial glands and focally in gastric epithelium. The negative tissues included pancreatic acini, Langerhans islets, hepatocytes and epithelium of bronchial, colonic and gall bladder origin. Hybridomas established after immunization of tumor cells secreted antibodies directed against a variety of human blood group antigens. They include Leb antigen and two types of precursor substances common to the ABH and Lewis system: type 1 with beta 1, 3 linkage and type 2 with beta 1, 4 linkage of terminal galactose to N-acetylglucosamine. Four other monoclonal antibodies are specific for B group substances. Three are directed against type 2 chain and one against both chains. (no Refs)

45. MONOCLONAL ANTIBODIES TO ANTIGENS OF HUMAN MELANOMA (MEETING ABSTRACT).

Brown JP, Hellstrom I, Hellstrom KE
No affiliation given
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Monoclonal antibodies were used to identify and characterize antigens of human melanoma. Spleen cells from mice immunized with melanoma cells were fused with mouse myeloma cells. The hybrids were screened both by binding assays and by immunoprecipitation. One of the most interesting antigens identified is p97, a 97,000 mol wt cell surface glycoprotein, which is present in most melanomas but in only trace amounts in normal adult tissue. However, certain fetal tissues contain significant amounts of p97. Monoclonal antibodies to a number of distinct antigenic determinants of p97 have been used to develop a 2-site immunoradiometric assay, to obtain syngergistic complement-dependent cytotoxicity, for preparation of immunotoxins and for imaging studies. P97 has been purified from detergent-lysates of cultured melanoma cells by affinity chromatography with monoclonal antibody and Staphylococcus aureus protein A coupled to Sepharose. Amino acid sequencing studies of the purified protein have revealed that the N-terminal amino acid sequences of p97 and transferrin are homologous. The structure homology of p97 and transferrin was confirmed serologically using a mouse antiserum to denatured p97. Like transferrin, p97 binds iron. We conclude that melanoma-associated antigen p97 is evolutionarily and functionally related to transferrin, although its exact role in melanoma cells remain to be elucidated. (no Refs)

46. CELL SURFACE ANTIGENS OF X-RAY INDUCED LYMPHOMA: DETECTION AND CHARACTERIZATION USING MONOCLONAL ANTIBODIES (MEETING ABSTRACT).

Allison JP
The University of Texas System Cancer Center, Science Park, Smithville, TX, 78957
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

The cell surface antigenic mosaic of an x-ray induced lymphoma of C57BL/6 mice has been examined using conventional and monoclonal antibodies. The tumor cells display four glycoproteins related to murine leukemia virus (MuLV) - two env and two gag gene products. Immunization of syngeneic mice with tumor cells elicited formation of antibodies to only one of the two MuLV env proteins. Analysis with monoclonal antibodies revealed that this antigen was antigenically related to ecotropic MuLV. One hybridoma clone, designated 124-40, produced by fusion of spleen cells from C6XL-immunized BALB/c mice with P3 myeloma cells, secreted monoclonal antibodies (McAb) which reacted with tumor cells, but not with normal lymphoid cells. The tumor associated antigen reative with McAb 124-40 was found to be a glycoprotein with subunit mol wt of approx 40 Kd, and was structurally and immunologically distinct from MuLV antigens on the tumor cells. The antigen was not found on adult spleen, thymus, bone marrow, or lymph node cells, nor on fetal thymus or spleen. Two additional x-ray lymphoma lines, as well as three spontaneous leukemias of AKR mice, were also unreactive with McAb 124-40. Administration of the McAB 124-40 to tumor-bearing mice resulted in a slight increase in survival time. The therapeutic effect was greatly enhanced by administration of McAb conjugated to the cellular toxin pokeweed antiviral protein. (no Refs)

47. MONOCLONAL ANTIBODIES TO HUMAN PROSTATE AND BLADDER TUMOR ASSOCIATED ANTIGENS (MEETING ABSTRACT).

Starling JJ, Wright GL
Eastern Virginia Medical School, Norfolk, VA, 23501
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston 55 pp., 1981.

Monoclonal antibodies to human prostate adenocarcinoma membrane antigens were produced by fusion of spleen cells from Balb/C mice immunized against the prostate cancer cells line DU145, and the P3X63/Ag8 mouse myeloma line. The hybrids were screened for antibody production using glutaraldehyde-fixed or live cells in an in vitro binding radioimmunoassay (RIA). Antibody binding specificity was also checked by quantitative adsorption studies. A hybridoma clone (83.21) was isolated that secreted antibodies which preferentially bound to prostate and bladder cancer cells but did not bind to a variety of other normal and malignant human cell lines. This antibody also reacted with a cytomegalovirus-transformed human embryonic lung cell line but not to normal human embryonic lung cells. Conventional and competitive binding studies indicate that the 83.21 monoclonal antibody does not bind to alpha-fetoprotein, carcinoembryonic antigen, prostatic acid phosphatase, human WBC antigen (HLA), beta2 microglobulin, fibronectin, prostate specific antigen or DR antigens. Preliminary immunoprecipitation data with 125I-labeled, detergent soluble, DU145 membrane proteins and the 83.21 monoclonal antibody suggest that this antibody binds two proteins with mol wt of 210 and 97 kilodaltons. (no Refs)

CLINICAL IMMUNOLOGY

48. CLINICAL SIGNIFICANCE OF CIRCULATING IMMUNE COMPLEXES IN PATIENTS WITH METASTATIC CANCER (MEETING ABSTRACT).

Krieger G, Kehl A, Bause I, Kneba M, Nagel GA
Medical University-Clinics,, Goettingen, W. Germany
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Two hundred and fifty patients with metastatic cancer (mainly breast cancer) have been followed clinically and by measuring circulating immune complexes using the C1q binding assay. Clinical follow up's and periodical determinations of C1q binding activity (cba) were performed at least for six mo. Sixty-four patients showed elevated levels of cba at least at one determination. There was no direct correlation between clinical course and levels of cba in tumor patients in contrast to a control group of patients with autoimmune diseases. However, there is some evidence, that the cba really represents immune complexes. Repeated freezing-thawing reduces significantly cba in patients sera and in sera with in vitro immune complexes but not in sera with added aggregated IgG. The C1q binding material could be precipitated at different polyethylene glycol (PEG) concentrations and was absorbed by protein A Sepharose. The absorbed material was separated into IgG and putative antigen by chromatofocussing. Further characterization has to be done in order to prove the immune complex nature of this material and its possible tumor specificity. (no Refs)

49. CIRCULATING IMMUNE COMPLEX AND IMMUNOLOGIC RESPONSES IN PATIENTS WITH MALIGNANT TUMORS.

Saiga T
First Dept. Surgery, Sch. Medicine, Gifu Univ., Tsukasa-cho, Gifu 500, Japan
Nippon Geka Gakkai Zasshi; 82(6):587-598 1981

One hundred forty-four patients with malignant tumors (gastric cancer, 60 patients; colorectal cancer, 42 patients; lung cancer, 32 patients; and breast cancer, 10 patients) were examined for circulating immune complex (CIC) by C1q solid-phase radioimmunoassay. They were tested for cellular and humoral immunity at the same time and the correlation of the responses with CIC was investigated. Positive CIC was obtained in 16 of the patients (11.1%), a high incidence being noted in patients with advanced cancer. Two of the 13 patients from whom the tumor was not completely removed showed persistent positive CIC postoperatively. The positive rate for delayed skin tests (tuberculin test and phytohemagglutinin response) was higher in patients with positive CIC than in those with negative CIC. No significant difference was observed in the T cell and B cell content between the positive CIC group and the negative CIC group, before or after surgery. Blast formation of lymphocytes showed a tendency to be lower in the positive CIC group than in the negative CIC group, before or after surgery. However, no significant difference was noted. No significant difference was observed in the CH50, C3 and C4 complement systems between the positive and negative CIC groups before surgery. After the operation, the positive CIC group had significantly higher C4 levels than the negative CIC group. No significant difference was observed in serum glycoproteins (alpha1-acid glycoprotein, alpha1-antitrypsin and haptoglobin) between the positive CIC group and the negative group, before or after surgery. Although CIC caused no significant differences in cellular immunity or humoral immunity, it is considered to be a factor which has some influence on them. (48 Refs) (In JPN)

50. GENERATION OF SUPPRESSOR CELLS FOR NATURAL KILLER (NK) ACTIVITY IN CANCER PATIENTS AFTER SURGERY (MEETING ABSTRACT).

Uchida A, Micksche M
Institute for Cancer Research, University of Vienna, Vienna, Austria
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Surgery often results in immunodeficiency and influences the incidence of metastases. NK cells seem to be important in host resistance against circulating tumor cells and therefore able to prevent the development of metastases. We are the first to demonstrate that human NK activity is regulated by suppressor monocytes in carcinomatous pleural effusion. We report here the effects of surgery on NK activity and its regulatory mechanisms in cancer patients. NK activity against K562 cells determined in a 4-hr chromium release assay of preoperative patients was comparable to that of normal donors. After surgery, NK activity of blood mononuclear markedly decreased, whereas lymphoproliferative response did not. Sephadex G 10 column passage of postoperative mononuclear cells gave no increase in cytotoxicity. When these monocyte-depleted cells were further cultured for 24 hr, they showed a significant increase in NK activity. Futhermore, NK activity of normal lymphocytes was suppressed by postoperative monocytes, while mitogenic response was not. This suppression of NK activity required 24 hr preculture of suppressor monocytes and NK effector cells but not the presence of monocytes in the cytotoxicity assay. Neither postoperative sera nor culture supernatants of postoperative monocytes were suppressive for NK cells. In addition, prostaglandins were not involved in monocyte-mediated suppression of NK cells. Immunotherapy with OK-432 was able to prevent reduction of NK activity and generation of NK suppressor cells after surgery. These results suggest that the appearance of suppressor monocytes in the circulation could be one cause of the depression of NK activity in cancer patients following surgery and this may be an indication to start with immunotherapy in the preoperative phase. (no Refs)

51. IMMUNE REACTIVITY IN CURED CANCER PATIENTS (MEETING ABSTRACT).

Samuelly B, Mekori T, Robinson E
Department of Oncology, RAMBAM Medical Center, Technion, Haifa, Israel
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Histochemical endotoxin stimulated nitrobluetetrazolium (NBT) test was performed on blood samples from 37 patients with breast cancer and 34 with various types of gynecological malignancies who were considered cured at the time of investigation. The disease free interval was 5-19 yr (median 7 yr) for breast cancer patients and 3-12 yr (median 6 yr) for patients with gynecological malignancies. NBT reduction by peripheral blood polymorphonuclear WBC in cancer patients (31.4 plus or minus 12.8 for breast cancer, and 29.0 plus or minus 12.78 for gynecological cancer) was significantly lower than in 41 controls (43.4 plus or minus 12.8. Forty of the above 71 patients were tested for skin reactivity to 5 recall antigens (purified protein derivative (PPD), Candidin, Trychphyton, Mixed Bacteria and Mumps). A hypoergic skin reactivity (complete anergy or a reaction to one antigen only) was found in 7/20 patients with breast cancer and in 8/20 patients with gynecological cancer compared to only 1/21 of the healthy controls. The differences between patients and control were statistically significant. No correlation was found between NBT reduction capacity and skin reactivity. Sixty-one patients were followed up for 1-4 1/2 yr (medain 1 3/4 yr). In 3 out of the 61 the disease has recurred. The results of this study indicate that immune abnormalities in cancer may persist also in the cured state. It is premature to determine whether this observation has any prognostic value. Further follow up is needed and more patients have to be tested in order to find out whether an impaired immune status is associated with an increased risk of developing recurrent disease and/or second primary neoplasm. (no Refs)

52. ISOLATION AND ELECTROPHORETIC ANALYSIS OF IMMUNE COMPLEXES FROM PATIENTS WITH BREAST CANCER.

Gilead Z, Troy FA, Sulitzeanu D
Lautenberg Center General and Tumor Immunology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel
Eur J Cancer Clin Oncol; 17(11):1165-1176 1981

Immune complexes (IC) were isolated from sera of patients with breast cancer (BC), from effusions from patients with breast and ovarian cancer (OC) and from effusions from patients with non-malignant diseases. Isolation was carried out with the aid of tubes coated with rheumatoid factor (RF) as immunoadsorbents. The effusions were first filtered through Sephacryl S-300 columns and the large mol wt material eluted in front of the IgG peak was used as the starting material, while most of the sera were processed without prior filtration. The IC eluted from the RF-coated tubes were radioiodinated and analyzed by electrophoresis on polyacrylamide gels, followed by autoradiography. Four putative IC-derived proteins were identified in the RF eluates and designated according to their mol wt (in Kdalton): p94, p46, p17 and p13. Protein94 was found in 1/8 BC effusions, but in none of the other samples tested; 'p46', which was actually a complex of several closely spaced proteins, was identified in at least 3/16 BC sera, 6/8 BC effusions, 3/4 OC effusions and 1/5 non-malignant effusions, but in none of 17 normal sera. The upper band of the complex seemed to be present mainly, if not exclusively, in effusions from patients with neoplasia. Protein17 and p13 were found more often and in higher concentrations in the malignant effusions. All of these proteins could be precipitated by treating the RF eluates with anti human Ig serum, suggesting that they were associated with Ig, presumably as immune complexes. (Author abstract) (35 Refs)

53. SUPPRESSOR CELL ACTIVITY OF FERRITIN-BEARING LYMPHOCYTES IN PATIENTS WITH BREAST CANCER.

Moroz C, Kupfer B
Rogoff-Wellcome Medical Res. Inst., Beilinson Medical Center, 49100 Petah Tikva, Israel
Isr J Med Sci; 17(9/10):879-881 1981

In patients with early stages (I, II) of breast cancer we identified a subset of circulating lymphocytes that carry ferritin on their surface. No such lymphocytes were identified in normal women nor in women with benign breast disease. These cells did not form spontaneous rosettes with sheep red blood cells. Further studies revealed that in vitro treatment of the patients' lymphocytes with levamisole resulted in the removal of the surface ferritin and in an increase in the reactivity of the lymphocytes in mixe d lymphocyte culture (MLC). Separation of the ferritin-positive lymphocytes from the E-rosetting T cells resulted in an increased reactivity of the patients' T cells in MLC. Readdition of the fraction containing the ferritin-positive cells to a mixed lymphocyte culture resulted in a decrease in the proliferative response of the patients' T lymphocytes. It is suggested that the ferritin-positive lymphocytes in breast cancer patients represent an active suppressor cell subset. (Author abstract) (13 Refs)

54. COOPERATIVE MULTI-INSTITUTIONAL STUDY ON IMMUNE RESPONSE (IMMUNOLOGICAL SKIN TEST) IN ESOPHAGEAL CARCINOMA PATIENTS - RESEARCH SOCIETY OF COMBINED IMMUNOTHERAPY IN ESOPHAGEAL CARCINOMA IN KYUSHU AND YAMAGUCHI DISTRICTS.

Inokuchi K, Sugimachi K, Okudaira Y, Yokoyama I, Sannohe Y, Kakegawa T, Nishi M, Tsuji Y, Tomita M, Ishigami K, Nomoto K
Second Dept. Surgery, Kyushu Univ. Sch. Medicine, Kyushu, Japan
Gan No Rinsho; 27(14):1713-1720 1981

Skin response tests were performed in 320 patients with esophageal cancer who were treated in eight different institutions from 1974-1979, and the results were compared with those of 30 healthy males. Relationship between skin response tests, immunotherapy, etc, and prognosis was also studied in 135 patients treated with immunotherapy and 168 patients who were not treated. Preoperative skin responses to purified protein derivative (PPD), phytohemagglutinin (PHA), Candida, and streptokinase-streptodornase (SK-SD) were significantly higher in the patients who had resectable esophageal carcinomas than in those with unresectable carcinomas, but compared to the healthy male controls, both groups of patients had significantly lower skin responses. Although responses to PPD were suspected to have some correlation to postoperative prognosis, responses to PHA were notably decreased usually, responses to Candida were elevated, and responses to SK-SD were low both before and after surgery, making any determination of correlation difficult. However, in spite of the general postoperative increases observed in responses to Candida, patients who died of early recurrence had low responses to Candida, thus that was thought to be an indicator of poor prognosis. A trend of increased survival rate was observed in patients with advanced stage esophageal carcinoma, suggesting clinical significance of immunotherapy. (5 Refs) (In JPN)

55. EFFECT OF ADJUVANT THERAPY ON SUPPRESSOR SYSTEMS IN PATIENTS WITH COLORECTAL CANCER (MEETING ABSTRACT).

Robinson E, Mekori T, Segal R
Department of Oncology, RAMBAM Medical Center, Technion, Haifa, Israel
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Two suppressor systems were studied in 34 healthy donors and 18 patients with co lorectal cancer Duke's B2 and C, by T-lymphocyte proliferation. The level of suppression in the induced suppressor system (ISS) was determined by the ratio of Thymidine incorporation by cells stimulated by suboptimal doses of Concanavalin A, 24 hr after incubation to the counts of cells stimulated at 0 time. Before therapy the number of tests expressing suppression or helper effect and their level was similar in patients and healthy controls. The patients were randomized after surgery into 2 groups, one being treated by radio-chemotherapy and the second by radio-chemotherapy and methanol extraction residue of BCG (MER). After chemo-radiotherapy the level of suppression level decreased while the increased and the level of the helper effect decreased. After chemo-radiotherapy + MER the number of tests showing suppression and their level decreased while the level of helper effect increased. The adherent cell suppressor system (ACSS) was tested by removal of the adherent cells on plastic petri dishes. The level of suppression was determined by the ratio of total lymphocyte proliferation to the proliferation of nonadherent cells. In patients with colorectal cancer the level of helper effect and suppression was higher compared to the controls. After treatment the number of tests showing helper effect as well as the level decreased. This was more pronounced in the radio-chemotherapy MER group compared to the radio-chemotherapy group. These results will be discussed in view of the results of a previous study showing a longer survival and disease-free interval in patients treated by chemo-radiotherapy + MER compared to those treated by chemo-radiotherapy alone. (no Refs)

56. 10. POSSIBLE MECHANISMS OF IMMUNOTHERAPY ACTION IN ACUTE NONLYMPHATIC LEUKEMIA: MACROPHAGE PRODUCTION OF COLONY-STIMULATING ACTIVITY.

Reizenstein P, Andersson B, Beran M
Div. Hematology, Dept. Medicine, Karolinska Hosp., S-104 01 Stockholm, Sweden
Recent Results Cancer Res; 80:64-69 1982

Earlier studies show that immunotherapy (IT) improves prognosis in acute nonlymphatic leukemia (ANLL), and that ANLL cells probably have tumor-associated antigens, for autologous lymphocytes can react to them. Also, IT seems to immunize against allogeneic ANLL cells, but there is no cross-immunity to autologous ones. Moreover, patients immunized against their ANLL cells have no better prognosis than patients not having lymphocytes reacting to their ANLL cells. It has also been suggested that IT causes nonspecific immunostimulation, but IT patients' lymphocytes actually react less than those of patients not given IT. The current hypothesis is macrophage activation: Lymphocyte suppression in IT could be explained by suppressor macrophages. Colony-stimulating activity, produced by bone marrow macrophages, decreases during remission in patients not given IT, but not in IT patients. Numerically, blood cells from pat ients given IT form more colonies than those from patients not given IT. Three of eight patients given IT had more colonies than the upper normal limit. (Author abstract) (16 Refs)

57. COMPARISON OF HLA PHENOTYPES IN LONG-TERM SURVIVORS WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH IMMUNOTHERAPY VERSUS CHEMOTHERAPY.

Tursz T, Hors J, Lipinski M, Amiel JL, Mathe G
Laboratoire d'Immunologie Clinique, Institut Gustave-Roussy, F-94800 Villejuif, France
Recent Results Cancer Res; 80:26-28 1982

Human leukocytic antigen (HLA) phenotypes were studied in children with acute lymphoblastic leukemia (ALL) who were alive without relapse greater than 8 yr after initiation of long-term chemotherapy (CT) or short-term chemotherapy followed by immunotherapy (IT). HLA determinations were of no prognostic value for CT patients. HLA AW33 and B17 antigens were increased significantly among IT patients, indicating prognostic value for HLA typing. (5 Refs)

58. IMMUNOCOMPETENCE AND MALIGNANT LYMPHOMA: IMMUNOLOGIC STATUS BEFORE THERAPY.

Anderson TC, Jones SE, Soehnlen BJ, Moon TE, Griffith K, Stanley P
Section Hematology Oncology, Dept. Internal Medicine, Univ. Arizona Coll. Medicine, Tucson, Arizona, 85724
Cancer; 48(12):2702-2709 1981

One-hundred-eighty-six previously untreated patients with malignant lymphoma were evaluated for immunocompetence by means of several tests of immune function: total circulating lymphocytes, T cells (E-rosettes), B cells (EAC-rosettes), delayed hypersensitivity to six recall antigens, serum immunoglobulins, mixed lymphocyte culture, and lymphocyte mitogenic response to phytohemagglutinin and pokeweed mitogen. The results were correlated with histology, stage, and clinical features. Diffuse lymphomas, especially diffuse histiocytic (large cell) (DHL), were associated with decreased absolute lymphocytes and E-rosette forming cells. Skin test reactivity varied with both histology and stage. For example, only one of six tests was impaired in diffuse lymphocytic well differentiated (DLWD) lymphoma in contrast to two of six in localized DHL and five of six in advanced DHL. Patients with nodular lymphoma exhibited depressed mean levels of IgA and IgG, while only IgA was significantly decreased in diffuse lymphoma. Mitogen stimulation was depressed in all groups, although mixed lymphocyte cultures did not differ significantly from controls. In summary, there is a spectrum of immunodeficiency of both B and T cell type in patients with malignant lymphoma that correlates with histology and stage. Implications and possible mechanisms of these observations are discussed. (Author abstract) (25 Refs)

59. CIRCULATING ANTI-ADRENOCORTICOTROPIN-ADRENOCORTICOTROPIN IMMUNE COMPLEXES IN PATIENTS WITH SMALL-CELL CARCINOMA OF THE LUNG (MEETING ABSTRACT).

Luster W, Gropp C, Havemann K
Department of Hematology and Oncology, University of Marburg, Marburg, W. Germany
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

The ectopic production of peptide hormones, partly marking paraneoplastic syndromes, in patients with lung cancer, especially in small-cell carcinoma, has been reported. Circulating immune complexes were described to be associated with small-cell carcinoma. Both phenomena may play a role in pathogenetic proliferation of this tumor. The present study was designed to investigate whether there is a correlation between these two findings. In sera of more than 190 patients with lung cancer of various histologic types ACTH was determined by radioimmunoassay. In 35% of all cases with small-cell carcinoma elevated ACTH levels were exhibited. In sera of those patients IgG-ACTH-immune complexes were isolated by affinity chromatography on protein A-sepharose or by polyethylene glycol precipitation. Though calcitonin is the peptide hormone, which shows the highest frequency associated with the small-cell carcinoma, there was no calcitonin immunoreactivity provable in the immuncomplex fraction. In sera of some patients without any demonstrable ACTH, free antibodies against ACTH were detected by titration in two radioimmunoassays. In patients with elevated ACTH levels before therapy, after response to therapy, a decrease of measurable ACTH corresponding with an increase of free ACTH-antibodies was shown. These results suggest that there is a connection between the ectopic production of autoimmunoreactive ACTH by a tumor and the formation of circulating ACTH-IgG immune complexes. (no Refs)

60. STUDY OF THE IMMUNITY MEDIATED BY CELLS IN 291 PATIENTS WITH MALIGNANT GENITOURINARY TUMORS.

Glait HM, Scorticati C, Feierstein JN, Bellora O, Koss A, Olivari AJ
Centro Oncologico de Medicina Nuclear, Instituto de Oncologia 'Angel H. Roffo', Buenos Aires, Argentina
Radiodiagn Radioter; 1(2):51-73 1981

Immunological states of 291 patients (14-88 yr old) with malignant genitourinary tumors (MGUT) were evaluated. Changes in the MGUT patients after hormonal treatment and radiotherapy were analyzed and were compared with changes in 27 patients that had benign urinary disease (BUD). The locations of the tumors were as follows: bladder (99), prostate (80), testicle (55), penis (20), kidney (28), and multiple (9). The following immunologic tests were performed: 2,4-dinitrochlorobenzene (DNCB), Candida antigen (CA), streptokinase-streptodornase (SK/SD), phytohemagglutinin (PHA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and circulating immune complexes (CIC). Every 3 mo different follow-up tests were performed depending on the location of the disease. The results for the BUD patients were as follows: DNCB (25 ug) positive (pos) in 48.1%, DNCB (100 ug) pos in 85.2%, CA pos in 48%, SK/SD pos in 59.3%, and blastic transformation normal in 68.4%. These results were lower than those for normal healthy persons. The results for the malignant tumor patients were presented according to location of tumor, stage of tumor, clinical evolution, use of radiotherapy, use of hormonal treatment, and histology (only in the cases of testicular seminoma). Correlation was observed between immunologic state and the evolution of the disease; this was most clearly demonstrated in non-patients with seminoma malignant tumors of the testicle, for whom the evolution of the disease and early diagnosis of relapse or metastases could be monitored. (36 Refs) (In SPA)

61. IMMUNE IMBALANCE AND IMMUNE MODULATION IN SOLID TUMOR PATIENTS: NEW INSIGHTS.

Serrou B, Cupissol D, Rosenfeld C
Laboratoire d'Immunopharmacologie des Tumeurs, Hopital Saint-Eloi, Centre Paul Lamarque, F-34033 Montpellier Cedex, France
Recent Results Cancer Res; 80:9-16 1982

Immune status in patients with solid tumors is reviewed. Several studies have found a variety of immunocomplexes (IC) that are present in increasing amounts during tumor growth or relapse (TGR) and in decreasing amounts following tumor reduction (TR). Because these complexes are apparently varied and poorly defined, practical use of IC measurements is limited. Changes in the plasma membrane lipid bilayer of WBC occur during TGR and disappear during TR. Plasma microviscosity may change in a similar fashion. Studies of patients treated with BCG have indicated that those with high levels of anti-BCG antibodies generally have a good prognosis, while those with low levels have a poor prognosis. A similar correlation has been found for vitamin A. Vitamin A apparently plays a role in cell differentiation and immune response. The T-gamma lymphocyte/T-mu lymphocyte ratio in patients increases during TGR and decreases during TR. A T-theophylline-resistant lymphocyte population that forms autologous rosettes is reduced during TGR and increases during TR. Suppressor-cell activity is affected by antiprostaglandins or irradiation and has therapeutic implications. Of new immunomodulating drugs, bestatin has antitumor activity in mice and RO-109359 increases cutaneous delayed hypersensitivity; results with interferon are unclear. (28 Refs)

62. REACTIVITY TO BCG AS AN ADDITIONAL PROGNOSTIC FACTOR IN PATIENTS WITH 'HIGH RISK' PRIMARY MALIGNANT MELANOMA (MEETING ABSTRACT).

Lejeune F, Cochran A, Buyse M, Macher E, Revuz J, Rumke P

No affiliation given

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

We report an analysis examining the prognostic importance of reactions of BCG as well as histological and clinical factors, in patients receiving BCG as an adjuvant treatment to surgery. One hundred and one patients with previously untreated 'high risk' - Clark levels III, IV, V - primary melanoma, prospectively received high dose BCG (6 x 10(8) viable units) id by heaf gun for 2 yr (EORTC protocol 18741) after uniform wide excision of the tumor. Univariate analysis of disease free interval (DFI) indicates that the degree of maximal reaction to BCG, Breslow thickness and Clark level are highly significant prognostic factors. When a multivariate model using Cox's proportional hasard regression was used for DFI, the degree of maximal reaction to BCG and Breslow thickness were by far the most significant criteria. A prognostic equation was thus derived to predict DFI from BCG max reaction and Breslow thickness. From scores calculations it appears that the two variables act independently and that this method allows the determination of predictive values which are highly discriminant (5 groups). This analysis was repeated on survival and gave similar results. It reveals the great prognostic importance of the degree of immune reactions of patients receiving immunotherapy, against BCG itself. This factor together with Breslow thickness has been integrated in a powerful predicting mathematical model for prognosis. (no Refs)

63. IMMUNOLOGICALLY DEFINED PROGNOSTIC SUBGROUPS AS PREDICTORS OF RESPONSE TO BCG IMMUNOTHERAPY.

Reid JW, Cannon GB, Perlin E, Blom J, Connor R, Herberman RB

Naval Regional Medical Center, Box 666, Portsmouth, VA, 23708

Recent Results Cancer Res; 80:219-226 1982

Fifty-two Stage I and II patients with non-small cell lung cancer were randomized after resection to no further therapy, BCG, or BCG plus allogeneic tumor cells. Patients have been observed for 16-65 mo (mean 39.5). When the two immunotherapy arms were combined and plotted against controls, trend analysis suggested (p = 0.088) an increase in disease-free interval (DFI) only for Stage I patients. The one-way mixed lymphocyte culture (MLC) values were depressed in some patients prior to any immune stimulation. Immunotherapy significantly benefited DFI among patients with a depressed MLC. (Author abstract) (11 Refs)

REVIEWS

64. BIOLOGIC-RESPONSE MODIFIERS AND ADJUVANT CHEMOTHERAPY: CONSIDERATION OF SELECTED PRECLINICAL INVESTIGATIONS IN RELATION TO CLINICAL POTENTIAL.

Goldin A, Chirigos MA, Macdonald JS, Fefer A, Mihich E

Div. Cancer Treatment, Cancer Therapy Evaluation Program, NCI, Bethesda, MD, 20205

Recent Results Cancer Res; 80:351-356 1982

Biologic-response modifiers (BRM) in adjuvant therapy are reviewed. BRM alter relationships between host and tumor and include agents that augment, modulate, or restore immunologic capacities, induce response modulators, affect tumor cell differentiation, and alter tumor cell susceptibility to immunologic destruction. BRM may be employed singly or in combination. Optimum therapy requires careful study of the effects of varying doses and delivery schedules on tumor response. Unlike active antitumor drugs, BRM frequently do not achieve optimum effect at the max tolerable dose. In combination therapy an antitumor agent may reduce the tumor cell population sufficiently that addition of BMR will allow the host's own defense mechanisms to eradicate residual tumor cells. BMR may thus combine with noncurative doses of antitumor agents to produce a curative effect. Surgery in combination with chemotherapeutic agents may have advantages including rapid reduction of tumor burden, immunosuppression, and increase in host drug-tolerance and tumor-cell sensitivity. Examples of BRM research are cited. (15 Refs)

65. ANTINEOPLASTIC PROPERTIES OF PYRIMIDINONE INTERFERON INDUCERS.

Stringfellow DA

Experimental Biology Res., Upjohn Co., Kalamazoo, MI, 49001

Adv Enzyme Regul; 19:335-348 1981

The interferon inducing, antiviral and antitumor activities of a new series of pyrimidinone compounds are compared and summarized in this report. A split in the mechanism of action exists in these compounds. One group represented by ABPP were very potent interferon inducing agents and the antiviral and antitumor activity of these agents correlated with their ability to induce interferon. The second group as exemplified by AIPP were not good inducers yet were just as active against virus infection and neoplastic disease. Presumably the split in antiviral and antitumor activity of these molecules was mediated by other host defense mechanisms as indicated by their ability to modulate various immune functions. The antitumor activity of the pyrimidinones was very dependent upon tumor load. If too high a tumor load was injected, the animals were not protected against the lethal consequences of the neoplastic disease. Although we presently do not know if interferon or interferon inducers will be effective in humans for the treatment of virus infections or neoplastic disease, ongoing studies should help answer these questions. The pyrimidinones are presently in preliminary clinical trials aimed at determining if they will induce interferon in humans and what effect they will have on various immune parameters. Results from these studies should provide answers as to the potential benefit of this interesting group of compounds. (25 Refs)

66. SURGICAL ADJUVANT THERAPY FOR LUNG CANCER.

Holmes EC
Div. Oncology, UCLA Sch. Medicine, Los Angeles, CA, 90024
Surg Clin North Am; 61(6):1289-1294 1981

Surgical adjuvant chemotherapy (SAC) and surgical adjuvant immunotherapy (SAI) are reviewed. Most studies of SAC have involved single chemotherapeutic agents such as cyclophosphamide, nitrogen mustard, methotrexate, and hexamethylenamine. More recently chemotherapy regimens containing various combinations of adriamycin, cyclophosphamide, vincristine, cis-platinum, and lomustine have been developed. The new and more effective combination chemotherapy has been evaluated in a surgical adjuvant setting. Most studies of SAI have involved BCG as an immunotherapeutic agent administered following surgical resection. BCG by three different routes, id, intrapleural, and intralesional, has been evaluated in the treatment of lung cancer (LC). Due to inaccurate intraoperative staging and frequent use of historical controls, interpretation of studies with id BCG is difficult. BCG given intrapleurally by way of chest tubes has not shown the expected effect. Intralesional BCG is capable of establishing potent systemic tumor immunity in animal models and induces regression of cutaneous malignant tumors in humans. Experience has indicated that endobronchial tumors can be injected safely with BCG; the form has promise since it is the most effective in animal models. Randomized studies with levamisole have been performed, but its precise role in treatment of lung cancer remains unclear. (27 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/117

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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CLINICAL TRIALS

1. ADJUVANT BCG TUMOUR ANTIGEN FOLLOWING PRIMARY TUMOUR RESECTION: RESULT OF MELBOURNE UNIVERSITY 5 YEAR STUDY (MEETING ABSTRACT).

Steward AM, Clarebrough JK, Wilson A

Departments of Surgery and Cardiothoracic Surgery, University of Melbourne, Melbourne, Australia

Clinical Oncology Society of Australia, November 24-27, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Thirty-four lung cancer patients have been entered by random assignment into a trial of adjuvant therapy using BCG (skin scarification) +/- autologous tumor antigenic preparation (subcutaneous innoculation), following resection of their primary tumor. All treated patients received 3-7 BCG doses at 2-4 weekly intervals, beginning 1 mo following operation. Six also received antigenic tumor preparation by hypertonic KCl fractionation. The treated group consisted of 11 Squamous, 3 Large Cell, 1 Adeno, and 2 Small Cell carcinomas. Controls were 7 Squamous, 6 Large Cell, 2 Giant Cell, 1 Adeno and 1 Small Cell. In the treated group, 7 out of 10 stage I and II are alive and well at 37-62 mo, compared with 2 of 11 controls plus 1 with metastases. Mean survival of those dying in the treated group was 30 mo, compared with 12.8 mo (control). In monitoring patient progress, serial plasma cyclic AMP (c-AMP) levels, serum T3 and thyroid stimulating hormone (TSH) were estimated in 5 patients from each group. Five patients who died within 15 mo, had c-AMP values of 1.1-9.2 Pmol/ml and 4 of these had falling T3 values. Five patients who remained alive and disease free at 16-31 mo had c-AMP values of 0.7-24.8 Pmol/ml, and static or rising T3 levels. Adjuvant therapy given to the treated group prolonged survival, disease free intervals, and appeared to improve quality of life. (no Refs)

2. RANDOMIZED CLINICAL STUDY ON INTRATUMORAL BCG-CELL WALL PREPARATION (CWP) THERAPY IN PATIENTS WITH SQUAMOUS CELL CARCINOMA IN THE HEAD AND NECK REGION.

Bier J, Rapp HJ, Borsos T, Zbar B, Kleinschuster S, Wanger H, Rollinghoff M

Dept. Maxillo-Facial and Plastic Surgery of the Face, Klinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, W. Germany

Cancer Immunol Immunother; 12(1):71-79 1981

Patients (10 female, 14 male; 52-86 yr old) with squamous cell carcinomas of limited size and spread were treated by intratumoral BCG-cell wall preparation (CWP) therapy in a randomized two-armed study. After a 3 yr observation period, the changes in BCG-CWP pretreated patients with respect to both complete tumor remission and survival expectancy were better than in surgically-treated patients. Side effects of BCG-CWP therapy were limited to moderate increases in temperature and pulse rate, some instances of slight chills and vomiting, and only short-term alterations in white blood cells. Neither significant immunological changes nor changes in liver, kidney, or other organ functions were observed. (44 Refs)

3. CLINICAL TRIAL OF CORYNEBACTERIUM PARVUM (INTRA-LYMPH-NODE AND INTRAVENOUS) AND RADIATION THERAPY IN THE TREATMENT OF HEAD AND NECK CARCINOMA.

Cheng VS, Suit HD, Wang CC, Raker J, Kaufman S, Rothman K, Walker A, Mcnulty P

Joint Radiation Oncology Center, Univ. Health Center of Pittsuburgh, 3601 Fifth Ave., Pittsburgh, PA, 15213

Cancer; 49(2):239-244 1982

Fifty-seven patients with previously untreated squamous cell carcinoma of the head and neck region of all clinical stages were entered a trial to evaluate the effectiveness of Corynebacterium parvum combined with radiation therapy in improving local and survival results. Twenty-nine patients were randomized to receive radiation therapy alone, and 28 patients were randomized to receive radiation therapy combined with C parvum. The C parvum was administered into the tumor-bearing lymph nodes of the neck or into the cervical node region in non-node-positive patients (4 mg/m2) and by intravenous routes (at 2, 2, 4, 4 and 4 mg/M2) at days-10,-7, and-3 before, and at +7 and +14 days after the start of radiation therapy. The study began in July 1975 and was terminated after 2 1/2 yr of patient accession. The statistical analysis showed that those receiving C parvum were not doing better than controls and, in fact, in some subgroups there was concern that they might be doing less well. Pertinently, analysis showed that those receiving C parvum would not experience the 25% point improvement in disease-free survival frequency which had been stipulated in the design of the protocol. (Author abstract) (29 Refs)

4. THERAPY WITH BCG AND DNCB FOR MELANOMA AND NEVUS BASAL CELL EPITHELIOMA.

Lubbe D, Zaumseil RP, Gstottner R

Hautklinik des Bereichs Medizin, Martin-Luther-Universitat Halle-Wittenberg, Ernst-Kromayer-Strasse 5-8, DDR-4020 Halle, E. Germany

Dtsch Gesundheitswes; 36(44):1854-1859 1981

Primary therapy of melanomas and basal-cell epitheliomas is a surgical problem. Because curative surgery, particularly in cases of malignant melanoma, is not always possible, adjuvant therapies such as immunotherapy and chemoimmunotherapy have been used. In a controlled clinical study of 66 patients with malignant melanoma, no relevant differences could be seen between results of purely surgical treatment and those of surgery with adjuvant therapy during a 40-mo follow-up period. In individual cases (malignant melanoma and nevus basal-cell epithelioma) impressive local tumor remission was achieved in part by local DCNB therapy. Indications for routine immunotherapy must be worked out in scientific studies. (25 Refs) (In GER)

5. LEVAMISOLE IN THE TREATMENT OF JUVENILE LARYNGEAL PAPILLOMATOSIS.

Schouten TJ, Bos JH, Bos CE, Van der Pot PJ, Van den Broek P

Div. Pediatric Oncology, Dept. Pediatrics, Juliana Children's Hosp., 's Gravenhage, The Netherlands

Int J Pediatr Otorhinolaryngol; 3(4):365-369 1981

Use of levamisole (2.5 mg/kg, po, 1-2x/wk) in the treatment of three patients with juvenile laryngeal papillomatosis is described. Levamisole treatment in the two patients in whom advanced disease necessitated tracheostomy produced no endoscopic evidence of improvement during 8-9 mo of treatment. The third patient was a 2-yr-old boy in whom papillomatosis was restricted to the larynx. The patient had undergone 13 previous surgical interventions followed by topical 5-fluorouracil treatment; tracheostomy was avoided by using nasotracheal intubation for approx 1 wk following each surgical procedure. After 22 mo of treatment with levamisole and homeopathic drugs, the vocal cords showed no papillomatous growth and were only slightly thickened. The last surgical intervention had taken place 12 mo previously. The results do not appear to justify a formal clinical trial on the effect of levamisole in juvenile laryngeal papillomatosis. (14 Refs)

6. TWO TRIALS WITH LEVAMISOLE IN ACUTE MYELOID LEUKAEMIA IN ADULTS (MEETING ABSTRACT).

Lehtinen M
Tampere Central Hospital, 33520 Tampere 52, Finland
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

The Finnish Leukemia Group has carried out two randomized trials to study the effect of Levamisole on remission duration in adult acute myeloid leukemia. In 1973-1976 the maintenance therapy consisted of daily 6-mercaptopurine (6-MP) and weekly Methotrexate (MTX) with or without levamisole, which was given on three consecutive days fortnightly. There is a statistically significant difference in favor of the Levamisole group with a p-value of 0.033. The remissions of four long term survivors on Levamisole have lasted from four to six yr. In the second trial 1978-1981 the maintenance therapy consisted of 6-thioguanine on four days and cytarabin on the fifth day every wk with or without Levamisole, which was given on the two cytostatic free days weekly. In March 1981, 11 patients in complete remission (CR) have been randomized to chemotherapy only, 15 patients to chemotherapy + Levamisole. Thirty-three percent (3/9) of the chemotherapy and 80% (12/15) of the Levamisole patients are in remission at 250 days. This difference is significant, but thereafter the number of patients is too small for statistical analysis. An analysis of the HLA-types, particularly HLA B12, has been started among the long term survivors in order to establish the possible relationship between HLA B12 and long term remissions in these two series. (no Refs)

7. CLINICAL RESULTS AND IMMUNOLOGICAL EVALUATION OF PATIENTS WITH ANLL RECEIVING AN INTERMITTENT CHEMOIMMUNOTHERAPY USING ALLOGENIC BLASTS PLUS NEURAMINIDASE (MEETING ABSTRACT).

Lutz D, Gruner H, Hirsch J, Stacher A
III Medical Department, Hanusch Krankenhaus, Vienna, Austria
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Remission of 16 patients with acute nonlymphocytic leukemia (ANLL) was maintained by an intermittent chemoimmunotherapy. Chemotherapy consisted of a 5-day treatment with cytosinarab inoside plus alternately either adriamycin or thioguanine or cyclophosphamide or lomustine (CCNU) at 4 weekly intervals. At day 15 after starting chemotherapy immunotherapy was administered of 2 x 10(9) allogenic leukemic blasts mixed with 5-50 units neuraminidase injected id at 18 different sites. Treatment was terminated after 3 yr of complete remission. Ten of the 16 patients relapsed most of them within 20 mo of first remission. Duration of first remission lasted between 3 and 49+ mo. Reproducibility of reversible changes during treatment cycles is more reliable for hematological parameters than for immunological parameters tested. Immunotherapy for maintaining remission was well tolerated but its improvement of clinical results is not yet ascertained. (no Refs)

8. INTERFERON IN THE TREATMENT OF ACUTE NON-LYMPHOCYTIC LEUKAEMIA IN ADULTS (MEETING ABSTRACT).

Vuopio P, Elonen E, Teerenhovi L, Ikkala E, Ruutu T, Cantell K
Department of Medicine, University of Helsinki, Helsinki, Finland
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Thirty-eight patients with acute non-lymphocytic leukemia treated with a high dose chemotherapy with thioguanine, cytosine arabinoside and daunorubicin (TAD) were randomly allocated and treated with or without interferon. Interferon was started on the next day after the first TAD induction course. Three million units interferon were given daily for one mo and qod until relapse. The maintanance treatment with thioguanine and cytosine arabinoside was given in both groups. Complete remission was achieved in 17 of 19 patients (89%) treated with and in 16 of 19 patients (84%) treated without interferon. Patients treated with interferon had more days with fever, granulocytopenia and thrombocytopenia as well as more frequently and more prolonged elevations in the serum alanine aminotransferase (ALAT) values. In April 1981 there were 6 of 17 patients with and 7 of 16 patients without interferon in remission. Twelve of 19 patients treated with and 9 of 19 patients treated without interferon are still alive. (no Refs)

9. DINITROCHLOROBENZENE IMMUNOTHERAPY OF RECURRENT SQUAMOUS PAPILLOMA OF THE CONJUNCTIVA.

Petrelli R, Cotlier E, Robins S, Stoessel K
455 Orange St., New Haven, CT, 06511
Ophthalmology (Rochester); 88(12):1221-1225 1981

The case history of a 24-yr-old man with a papilloma that was refractory to electrocautery, surgical excision, and cryosurgery but which eventually responded to several treatments with dinitrochlorobenzene (DNCB) is reported. The patient first presented in July 1977 with 'irritating polyps' of the right eye. After electrocautery was unsuccessful, surgical excision was tried twice and failed, a nd cryosurgery was attempted in February 1978, but the papilloma continued to increase in size to a fulminant growth. Sensitization finally occurred after a repeat application, and DNCB was applied to the tumor surface at a dosage of 2.5 mg/ml acetone, followed by subconjunctival injections of a small amount of DNCB with a tuberculin syringe 4 wk after the initial treatment. Seven DNCB treatments performed over 8 wk resulted in a 50% reduction in mass size, but the patient did not return for treatment until March 1979, with the mass enlarged. Six more treatments in the next 2 mo were followed by another period of patient absence, but upon return at the end of 10 mo the papilloma was gone and only some hyperemia of the medial canthus was visible. The relatively high DNCB concentration was tolerated well, and minor irritation was treated with analgesics, topical antibiotics, and topical steroids. (9 Refs)

10. IMMUNOSTIMULATION BY SYSTEMIC ADMINISTRATION OF PROPIONIBACTERIUM GRANULOSUM IN PATIENTS WITH PRIMARY OR SECONDARY LUNG TUMOURS.

Roszkowski K, Gil J, Roszkowski W, Szmigielski S, Nowakowski W, Ko HL, Pulverer G, Jeljaszewicz J
Postgraduate Medical Center, Warsaw, Poland
Eur J Respir Dis; 62(6):425-433 1981

The effect of a cell suspension of Propionibacterium granulosum strain KP-45 given intravenously to patients with advanced primary or secondary lung carcinoma, and simultaneously treated with cytostatic drugs, was estimated. The control group consisted of patients treated with cytostatics only. The clinical state of patients treated with the KP-45 preparation and with this immunostimulant plus cytostatics, was compared by evaluation of tumor size by x-ray examination, peripheral blood picture, and biochemical and immunological parameters. Treatment with P granulosum KP-45 did not cause any serious adverse reaction or complication. No evident inhibitory effect on primary or secondary lung tumor development was observed. However, injections of the KP-45 preparation in cytostatics-treated patients resulted in decreased adverse effect of these drugs on the hemopoietic system and absence of bacterial infections, in contrast to patients treated with cytostatics only. (Author abstract) (18 Refs)

11. SURGICAL ADJUVANT THERAPY FOR MALIGNANT MELANOMA.

Pinsky CM, Oettgen HF
Clinical Immunology Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Surg Clin North Am; 61(6):1259-1266 1981

A clinical trial evaluated the effect of Corynebacterium parvum on recurrence and survival rates and on immunologic functions in 43 patients with regionally metastatic malignant melanoma who were free of disease after surgery. C parvum, inactivated by heat and formaldehyde, was used at a concentration of 7 mg/ml. Patients first received a daily dose of 4 mg C parvum iv over 30 min for 5 conse cutive days. Following discharge from the hospital, treatment was continued with 4 mg C parvum sc weekly during yr 1, every other wk during yr 2, and monthly in yr 3. Estimated time to recurrence was significantly shorter in these patients than in others treated with BCG. Although neither BCG nor C parvum seem to improve the outcome expected from surgery alone, the results provide a basis for comparison with new therapies. (13 Refs)

12. MELANOMA: ADJUVANT CHEMO-IMMUNOTHERAPY WITH D.T.I.C. AND B.C.G. FAILS TO IMPROVE SURVIVAL (MEETING ABSTRACT).

Schaerer R, Swiercz P, Mousseau M, Beani JC, Reymond JL, Amblard P
Unite de chimiotherapie, C.H.R. University de Grenoble, 38700 La Tronche, France
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Thirty-four evaluable patients with a cutaneous malignant melanoma (MM) at a loco-regional stage have been treated by local wide excision. Staging included the determination of: 1) the level of invasion, 2) the thickness of the lesion and 3) the clinical stage by a minimal node dissection. Adjuvant treatment consisted with Pasteur fresh BCG (150 mg/wk with the heafgun) for one yr, for every patient from level III through level V. In patients with level IV and V lesions the treatment began with three monthly courses of dacarbazine (DTIC) (250 mg/m2/d x 5 d). Some modifications were accepted when necessary and were not considered as causes of exclusion; then protocol modalities were respected in the range of 80% of the cases. There were 6 relapses before and 2 relapses after completion of treatment. Six patients died, 5 by metastatic spread, 1 by an accident. The median observation period is 29 mo. The actuarial survival is 82% at 24 mo and 75% at 36 mo. These results do not differ from those as observed in control patients in similar studies from the literature and do not confirm the benefit of BCG as an adjuvant treatment in MM. (no Refs)

13. SPECIFIC IMMUNOTHERAPY WITH VACCINIA ONCOLYSATES.

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Cancer Immunol Immunother; 12(1):1-4 1981

A preliminary trial of live vaccinia virus-augmented lysed tumor cell vaccine (vaccinia oncolysate) was conducted; 29 patients with overwhelming metastasis after resection of primary tumor were given a dose of 5 x 10(6) vaccinia oncolysate/ml every wk for 6 mo and every 2 wk for 18 mo or until progression. The treatment was tolerated well, but 20 patients died during the trial. Nine patients seemed to develop stable disease; all of them had repeated delayed hypersensitivity responses to the vaccine, as did about half of the patients who did not survive. (10 Refs)

SYNTHETIC IMMUNOTHERAPEUTIC AGENTS

14. ISOPRINOSINE AS AN IMMUNOPOTENTIATOR IN AN ANIMAL MODEL OF HUMAN OSTEOSARCOMA.

Tsang KY, Fudenberg HH

Dept. Basic and Clinical Immunology and Microbiology, Medical Univ. South Carolina, Charleston, SC, 29425

Int J Immunopharmacol; 3(4):383-389 1981

Immunostimulating capacity of isoprinosine (ISO) was investigated in normal and human osteosarcoma (OS)-bearing hamsters. In vitro concanavalin A (Con A)-induced lymphocyte proliferation was increased over control levels at all ISO concentrations tested (10, 20, 50, and 100 ug/ml medium) in both control and OS-bearing animals and was greater in OS-bearing hamsters (58-107%) than in normal hamsters (23-49%). On days 1, 3, and 5 following in vivo administration of ISO (23 or 5 mg/kg, ip) in both normal and OS-bearing hamsters, in vitro Con A-induced lymphocyte proliferation and natural killer cytotoxicity were increased; levels returned to control values on day 7. Before treatment, monocyte chemotactic responsiveness (MCR) was significantly lower in the OS group than in the normal group. However, 1, 3, and 5 days following ip injection of 2 mg/kg of ISO in OS-bearing hamster, MCR was significantly enhanced compared to similar hamsters which received only saline. Results indicate that ISO produces a generalized enhancement of immune function in hamsters with OS and suggest that the drug may be beneficial to human cancer patients. (29 Refs)

INTERFERON

15. REVIEW OF EXPERIENCE WITH INTERFERON AND DRUG SENSITIVITY TESTING OVARIAN CARCINOMA IN SEMISOLID AGAR CULTURE.

Epstein LB, Marcus SG
Cancer Res. Inst., Univ. California, San Francisco, CA, 94143
Cancer Chemother Pharmacol; 6(3):273-277 1981

Studies were performed with a semisolid agar culture system to determine the in vitro sensitivity of human ovarian carcinoma to human leukocyte interferon (IFN-alpha) and standard chemotherapeutic agents (adriamycin, cis-platinum, hexamethylmelamine, melphalan, and velban). Growth in culture occurred in 67% of samples derived from ascitic fluid. Seventy-one percent of samples exhibited reduction in tumor colony number greater than 25% in response to 300 units IFN/ml. The responsiveness of the tumor cells to interferon ran parallel to their overall responsiveness to the other chemotherapeutic agents. Sensitivity to interferon was not related to the histology or grade of the tumor or to the stage of the disease. The mean value for the percentage of viable cells in the ascitic samples (89%) was considerably higher than in solid tumor samples (39%). The mean percentage of tumor cells in the ascitic samples (28%) was considerably lower than of the solid tumor samples (81%). Colonies from ascitic fluid were more sensitive to the antiproliferative effects of interferon than the colonies form solid tumor samples. Analysis of drug testing showed that in 5 8% of 12 evaluable situations when a positive response in vitro was given, stabilization or regression of the tumor occurred in vivo after treatment with the drug. The studies could be used for assessing whether various types of interferon have the same degree, range, and mechanism of action of antitumor effect. (18 Refs)

16. DEPRESSION OF NATURAL KILLER CELL ACTIVITY BY INTERFERON.

Ho M, White LT, Haverkos HW, Breinig MC, Pazin GJ, Armstrong JA
Univ. Pittsburgh, Pittsburgh, PA
J Infect Dis; 144(6):605 1981

Over a 5-mo period, a 37-yr-old man with multiple warts received 55 im or intralesional injections of human leukocyte interferon (HuIFN-alpha). During the first 5 wk of therapy in vitro incubation with HuIFN-alpha increased the natural killer (NK) cell activity of mononuclear WBC from the peripheral blood of the patient. The NK cell activity of WBC from 10 of 11 normal, untreated subjects was increased to a similar extent by in vitro incubation with HuIFN-alpha. During the next 17 wk of therapy, incubation of the patient's WBC with HuIFN-alpha did not increase NK cell activity when compared with activity of WBC incubated without HuIFN-alpha; in 17 of 28 assays with the patients's WBC, depression of NK cell activity was observed. After therapy was discontinued, NK cells were again stimulated by HuIFN-alpha. Initially, circulating NK cell activity was occasionally stimulated 5 hr but not 24 hr after injections of HuIFN-alpha. In all of five tests from week 14 to week 22, circulating NK cell activity was depressed 5 hr and 24 hr after injection of 2.4 x 10(6) units of HuIFN-alpha when compared with activity before injection. Einhorn et al showed that levels of circulating NK cell activity were depressed 6 hr but stimulated 24 hr after injection of HuIFN-alpha. After prolonged therapy acute depression of levels of circulating NK cell activity was observed in our patient, a depression that could also be demonstrated by in vitro incubation of WBC with HuIFN-alpha. In spite of this evidence of in vitro and immediate in vivo depression of NK cell activity by HuIFN-alpha, circulating NK cell activity measured more than 24 hr after injection was elevated. Whether this result reflects a slow long-term effect of HuIFN-alpha remains to be determined. (1 Ref)

17. LYSIS OF FRESH HUMAN B-LYMPHOCYTE-DERIVED LEUKEMIA CELLS BY INTERFERON-ACTIVATED NATURAL KILLER (NK) CELLS.

Pattengale PK, Gidlund M, Nilsson K, Sundstrom C, Sallstrom J, Simonsson B, Wigzell H

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Int J Cancer; 29(1):1-7 1982

Fresh neoplasic B cells from 14 untreated patients with naturally occurring B-cell leukemias were found to be susceptible to lysis by human natural killer (NK) cells. The observed lysis of the fresh, non-cultured, neoplastic B cells was mediated by a population of interferon-augmentable, FcR-positive, non-adherent lymphoid cells, which were also able to kill the 'standard' NK target K562. A further finding was the correlation of NK susceptibility with disease available in 11 patients with chronic lymphocytic (CLL) and one patient with lymphosarcoma cell leukemia (LSCL). Enriched neoplastic B cells from seven untreated patients with non-progressive CLL, whose disease activity was stable throughout the 6 mo period of study, exhibited persistent and essentially unchanged NK susceptibility profiles. In contrast, four untreated patients with progressive CLL also had a measurable fraction of NK-susceptible, neoplastic targets, but these cells subsequently disappeared after successful cytoreductive therapy, and later re-emerged when these patients again developed progressive disease. Furthermore, one patient with LSCL was found to have persistent, measurable NK susceptibility in his tumor-enriched fraction after unsuccessful cytoreductive therapy. An additional finding in the peripheral blood of patients with chronic B-cell leukemias was the presence of significantly lower NK effector-cell activity against K562 as compared to normal donor peripheral blood lymphocytes (PBLs). The implications of these findings are discussed. (Author abstract) (25 Refs)

18. EFFECT OF ACYCLOVIR AND INTERFERON ON HUMAN HEMATOPOIETIC PROGENITOR CELLS.

Parker LM, Lipton JM, Binder N, Crawford EL, Kudisch M, Levin MJ

Div. Medical Oncology, Sidney Farber Cancer Inst., Boston, MA, 02115

Antimicrob Agents Chemother; 21(1):146-150 1982

Continuous in vitro exposure of human bone marrow cells to acyclovir (approx 200 uM) or human leukocyte interferon (approx 250 U/ml) caused 50% inhibition of granulocyte colony-forming cell differentiation. Colonies expressed in the presence of either agent were reduced both in size and number. Erythroid progenitors were more resistant than granulocyte progenitors to the antiproliferative effects of acyclovir. Progenitor cells of patients recovering from cytotoxic chemotherapy were not more sensitive to the effects of acyclovir or interferon than were cells obtained from patients before chemotherapy. (Author abstract) (26 Refs)

19. A COMPARISON OF THE ANTIPROLIFERATIVE AND ANTIVIRAL ACTIVITIES OF ALPHA-, BETA- AND G-INTERFERONS: DESCRIPTION OF A UNIFIED ASSAY FOR COMPARING BOTH EFFECTS SIMULTANEOUSLY.

Elfe R, Hahn T, DeTavera M, Schertel F, Holtmann H, Elfe G, Levin S
Kinderklinik der Universitat Munchen, Munich, W. Germany
J Immunol Methods; 47(3):339-347 1981

An assay system is described which allows simultaneous measurement of antiviral (AV) and antiproliferative (AP) activities of various interferons (IFNs) with the same indicator cells and tests one biological function, ie the reduction of DNA synthesis. Human interferon-alpha, interferon-beta, and interferon-gamma preparations were investigated for their respective AV and AP activities. In repeated independent experiments the AP:AV ratio was found to be constant for each interferon preparation. However, a striking difference in the AP:AV ratios was found between the preparations, being highest in IFN-gamma and lowest in IFN-alpha. The validity of this assay was substantiated by the observation that the AP activity of the IFNs is not influenced by virus once the cells are protected by sufficient amounts of IFN and that the score of the microscopically assessed cytopathic effect (CPE) strongly correlates with the reduction of [3H]TdR uptake in the cultures. The AP:AV ratio of a Corynebacterium parvum induced IFN resembled that of the IFN-alpha-reference, suggesting that contrary to previous reports, the C parvum induced IFN is of alpha type. It is suggested that the assay system presented here provides a simple means not only of comparing AP and AV ratios of various IFNs but also of characterizing IFNs of unknown type. (Author abstract) (23 Refs)

20. ALTERED PHARMACOLOGICAL PROPERTIES OF LIPOSOME-ASSOCIATED HUMAN INTERFERON-ALPHA.

Eppstein DA, Stewart WE
Inst. Bio-Organic Chemistry, Syntex Res., Palo Alto, CA, 94304
J Virol; 41(2):575-582 1982

Human interferon-alpha was associated in different ways with positively (stearylamine) and negatively (phosphatidylserine) charged phosphatidylcholine multilamellar vesicles, depending on the presence or absence of a cholesterol component. Inclusion of cholesterol resulted in interferon that was significantly (p = 0.0001) more deeply internalized within the liposomes, such that detergent disruption was necessary before most of the interferon activity was expressed. Interferon was stably associated with stearylamine-containing liposomes, both with and without a cholesterol component. However, inclusion of cholesterol in the phosphatidylserine-containing liposomes was necessary for stable association of the interferon for more than 2 days at 4 C or for more than 24 hr at 37 C. After intramuscular injection into mice, liposome-associated interferon in reverse-phase evaporation vesicles was retained at the local site of injection significantly longer than free interferon. Even 3 days after intramuscular injection, stearylamine-containing liposomes with or without cholesterol resulted in local interferon levels that were comparable to the peak levels obtained 2 to 4 hr after free interferon was injected. In contrast, free interferon was not detectable in the local muscles 24 hr after injection of 104.6 U. Liposomes containing phosphatidylserine and cholesterol resulted in intermediate levels of local interferon retention; without a cholest erol component, phosphatidylserine-containing liposomes resulted in no increased local interferon retention compared with the results when free interferon was injected. (Author abstract) (22 Refs)

21. ENHANCED EXPRESSION OF MELANOMA-ASSOCIATED ANTIGENS AND BETA2-MICROGLOBULIN ON CULTURED HUMAN MELANOMA CELLS BY INTERFERON.

Liao SK, Kwong PC, Khosravi M, Dent PB
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JNCI; 68(1):19-25 1982

The effect of human leukocyte interferon (IFN) on the in vitro growth and expression of melanoma-associated antigens (MAA), beta2-microglobulin (beta2m) and HLA-DR antigen on cultured human melanoma cells was studied. Exposure of melanoma cells to IFN for 64 hours resulted in a dose-dependent inhibition of growth with 46% reduction in cell number at 10(3) U IFN/ml and 74% reduction at 10(5) U/ml. Quantitative absorption experiments in the mixed hemadsorption assay determined that the expression of MAA and beta2m on treated cells was enhanced at 10(2) -10(5) U IFN/ml, twofold to fivefold for MAA and fivefold to twelvefold for beta2m. No change was seen in HLA-DR antigen expression. The IFN-induced enhancement of MAA and beta2m could be detected as early as after 16 hours and a maximum expression was reached at 96 hours after IFN exposure. The IFN-induced enhancement of MAA and beta2m on melanoma cells was reversible. Studies with melanoma cells grown in stationary phase and serum-deprived conditions indicated that IFN-induced augmentation of MAA and beta2m did not require cell proliferation. The data suggest that the effect of IFN on antigen expression is independent of its effect on cell growth. Further studies are needed to fully elucidate the mechanism. (Author abstract) (42 Refs)

22. MEASUREMENT OF ANTITUMOR AND ADJUVANT EFFECTS OF INTERFERON WITH TRANSPLANTABLE AND OTHER TUMORS IN MICE.

Chirigos MA
Lab. Chemical Pharmacology, Div. Cancer Treatment, NCI, NIH, Bethesda, MD, 20205
Methods Enzymol; 79:414-419 1981

The effects of interferon (IF) on experimental mammary adenocarcinoma (MAC) line 16/C and leukemia (MBL-2) cells are described, with emphasis on the cytoreductive effect of IF. Response of MAC to IF and IF inducers was determined in four groups of B6C3F1 female mice inoculated sc with 1 x 10(7) 16/C cells treated as follows: phosphate-buffered saline (control), IF (100,000 units), Pyran (MVE-6: 8 mg/kg), or BruPel (8 mg/kg). Intralesional treatments (id injections around the the tumor site) were given starting on day 3 and continued daily for 18 days. Tumor sizes were greatest in the control mice, followed by those treated with IF, MVE-6, and BruPel. Mean survival times (in days) were 24, 40, 55, and 40, respectively. In the assay of in vivo antitumor activity, MBL-2 leukemic ascites cells were inoculated ip in C 57/BL/6 male mice and groups were treated with a test agent starting on day 1 and continued daily for 5 days: bovine serum albumin (BSA, 0.5 mg), IP (100,000 units), or MVE-6 (0.2 mg). Each group was divided into mice used to determine tumor-induced death rates and those sacrificed (at day 6) to provide macrophages for use against fresh MBL-2 cells. The in vivo evaluation yielded the following mean survival times in days: control, 18; BSA, 23; IF, 38; and MVE-6, 48. In vitro tumor cell deaths (percent) were: BSA, 25; IF, 52; and MVE-6, 80. Macrophages harvested from these treated groups, and incubated in vitro with freshly prepared MBL-2 tumor cells, had a significantly greater tumoricidal effect than those from the placebo-treated group. It is suggested that the IF antiproliferative effect on tumor cells may be a direct effect, or an enhancement of cellular immune responses by direct activation of natural macrophage and natural killer cell tumoricidal activity. (16 Refs)

23. MEASUREMENT OF INTERFERON EFFECTS ON MURINE LEUKEMIA VIRUS (MULV)-INFECTED CELLS.

Pitha PM
Biochemical Virology Lab., Johns Hopkins Oncology Center, Baltimore, MD, 21205
Methods Enzymol; 79:422-432 1981

Assays of infectious murine leukemia virus (both ecotropic and xenotropic), suitable for measuring interferon effects, are reviewed. Cell-free virus assay, infectious centers assay, in situ infectious assay, and syncytia induction in XC cells (rat tumor line) are described for ecotropic viruses. For xenotropic viruses, the assay for MSV (murine sarcoma virus), virion-associated reverse transcriptase, radioisotope labeling of virus particles, and virus purification, are discussed. Chromatographic purification of viruses, isolation of virus RNA and its analysis by gel electrophoresis, and separation and identification of virion proteins are reviewed. Assays of viral RNA and protein in infected cells, including methods of preparation, nucleic acid hybridization, northern blotting technique, and competitive radioimmunoassay, are also reviewed. (32 Refs)

24. PREPARATION OF ANTIBODIES TO HUMAN LYMPHOBLASTOID INTERFERON.

Smith ME
Lab. Chemical Biology, Natl. Inst. Arthritis, Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, MD, 20205
Methods Enzymol; 79:567-570 1981

Methods are described for producing antibodies to partially purified and homogeneous human lymphoblastoid interferon (HLIF) by immunization of sheep and rabbits. The resulting material is useful in immunoadsorbent affinity chromatography for purification of HLIF. Monospecific antibodies to the 18,500 dalton component of HLIF has been prepared in large quantities by immunization of a single sheep. (12 Refs)

25. ANALYSIS OF INTERFERON MRNA IN HUMAN FIBROBLAST CELLS INDUCED TO PRODUCE INTERFERON.

Raj NB, Pitha PM
Oncology Center, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Proc Natl Acad Sci USA; 78(12):7426-7430 1981

The levels of interferon mRNA as a function of interferon induction by poly(rI)-poly(rC) in human fibroblast cells were determined by RNA hybridization using a cloned beta interferon cDNA and by translation in Xenopus oocytes. Whereas previous studies analyzed mixtures of interferons, the availability of the cloned beta interferon cDNA and the antiserum to purified beta interferon enabled us to focus on the expression of only one class (beta) of interferon genes. The induction of interferon synthesis depends primarily on the accumulation of interferon beta mRNA in the cells, and the interferon beta mRNA rapidly disappears several hours after its appearance in the cytoplasm. No detectable interferon beta mRNA sequences are present in uninduced cells. The degradation of interferon beta mRNA in the induced cells requires ongoing protein synthesis; accumulation of interferon beta mRNA was observed in the continuous presence of cycloheximide. The interferon beta mRNA detected at the early stages of induction is 1,100 nucleotides long and its size progressively decreases with time. By both the hybridization and the translational assay in Xenopus oocytes, only one size of interferon beta mRNA and one species of beta interferon could be identified. (Author abstract) (33 Refs)

26. HUMAN LYMPHOCYTE PRODUCTION OF CORTICOTROPIN AND ENDORPHIN-LIKE SUBSTANCES: ASSOCIATION WITH LEUKOCYTE INTERFERON.

Smith EM, Blalock JE
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Proc Natl Acad Sci USA; 78(12):7530-7534 1981

Human leukocyte interferon (hIFN-alpha) preparations contain immunologically and biologically recognizable endorphin and corticotropin-like (ACTH-like) activities. The ACTH bioactivity was demonstrable only after pepsin or acid treatment. Highly purified hIFN-alpha was composed of two molecular species of interferon (18,500 and 23,000 daltons). Endorphin activity was associated with both of these molecules. Pepsin treatment of the 23,000-dalton but not the 18,500-dalton hIFN-alpha generated ACTH activity. In acid, the 23,000-dalton hIFN-alpha broke down into the 18,500-dalton form and ACTH (4,500 daltons). The ACTH derived from hIFN-alpha by pepsin digestion comigrated with a purified ACTH standard in NaDodSO4/polyacrylamide gel electrophoresis. hIFN-alpha-producing lymphocytes showed positive immunofluorescence after staining with highly specific antisera to ACTH-alpha-(1-13) and gamma-endorphin. Essentially 100% of the human peripheral lymphocytes were capable of producing both ACTH and gamma-endorphin-related substances, presumably associated with hIFN-alpha. These results strongly suggest a circuit between the immune and neuroendocrine systems which involves neuroendocrine hormone-like substances, some of which are associated with hIFN-alpha. (Author abstract) (27 Refs)

INTERFERON INDUCING AGENTS

27. STUDIES ON THE ANTITUMOR ACTIVITIES OF PYRIMIDINONE-INTERFERON INDUCERS. I. EFFECT AGAINST ARTIFICIAL AND SPONTANEOUS LUNG METASTASES OF MURINE TUMORS.

Milas L, Hersh EM, Stringfellow DA, Hunter N
Dept. Experimental Radiotherapy, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
JNCI; 68(1):139-145 1982

Since pyrimidinone compounds induce interferon production in several animal species and have potent antivirus activities, it appeared important to determine whether these compounds could also induce antitumor activities in their recipients. Pyrimidinone compounds 2-amino-5-bromo-6-methyl-4-pyrimidinone (ABMP), 2-amino-5-bromo-6-phenyl-4-pyrimidinone (ABPP), and 2-amino-5-iodo-6-phenyl-4-pyrimidinone (AIPP) were studied for their activities against artificial lung metastases of the weakly immunogenic spontaneous fibrosarcoma NFSa, the moderately immunogenic spontaneous mammary carcinoma MCa-K, and the strongly immunogenic 3-methylcholanthrene-induced fibrosarcoma FSa syngeneic to inbred

C3Hf/Kam mice. In addition, the therapeutic efficacy of ABPP and AIPP was also determined against spontaneous lung metastases of NFSa. ABPP and AIPP given ip at 250 mg/kg for 2 or 3 consecutive days before or after iv inoculation of NFSa, FSa, or MCa-K cells greatly reduced the number of tumor nodules developed in the lungs. ABMP, however, was considerably less effective. ABPP and AIPP were also effective in therapy of spontaneous lung metastases of NFSa, especially when these compounds were given before surgical removal of the primary tumor. Neither ABPP nor AIPP was effective against tumor nodules growing in whole-body irradiated (WBI) mice, but both protected mice against enhancement of lung metastasis formation induced by exposure to whole-body irradiation. ABPP was more effective than in AIPP in inducing production of interferon in normal mice. When treated with ABPP, WBI mice, however, were unable to produce interferon. These results show that 6-phenyl-pyrimidinone compounds induce strong antitumor activities in mice, which correlated with neither tumor immunogenicity nor the ability of these agents to induce interferon, but which depended on the immune status of the tumor host. (Author abstract) (29 Refs)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

28. SELECTIVITY IN THE EFFECTS OF INDOMETHACIN ON BCG-ACTIVATED SUPPRESSOR CELL POPULATIONS.

Bennett JA, Kemp JD, Mitchell MS, Rao VS

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J Immunopharmacol; 3(2):221-239 1981

Indomethacin (IND) and the related compounds salicylate (salicylic acid), aspirin, and RO3-1314 were tested on BCG-induced macrophage-like suppressor cells from the spleen (S) and their precursors from the bone marrow (BM) of female C57BL/6 mice. In vitro immunization of S cells with irradiated P815 mastocytoma was prevented by pretreatment of S donor mice with BCG. All four drugs, when added at the initiation of coculture, almost completely blocked the inhibition of immunization produced by BCG-stimulated cells. IND was most effective: it was inactive at concentrations less than 10(-7) M while at concentrations greater than 10(-5) M it was itself immunosuppresive. Exposure to IND throughout the immunization culture period was more effective in blocking suppressor cells than shorter exposure, and the later IND was added the less was its blocking effect. The inhibitory activity of BCG-induced splenic suppressor cells was primarily in the nylon wool-adherent cells; IND inhibited suppressor activity in both adherent cells and unfractionated S cells. BM cells from BCG-treated mice were twice as suppressive as those from normal mice, but IND was not as effective in blocking the suppressor effect as it was with S cells. Nylon wool-adherent BM cells were more immunosuppressive than nonadherent cells; cells from both normal and BCG-treated mice suppressed immunization of normal cells. Immunosuppressive ability of adherent BM cells from both normal and BCG-treated mice was partially blocked by IND. While suppression generated by nonadherent marrow from normal mice was partially blocked by IND, it was ineffective on BM cells from BCG-treated mice. (37 Refs)

29. EXPERIMENTAL SCREENING OF TWO BCG PREPARATIONS PRODUCED ACCORDING TO DIFFERENT PRINCIPLES. IMMUNOSTIMULATING PROPERTIES, SAFETY, AND ANTITUMOR ACTIVITY.

Kreeftenberg JG, De Jong WH, Ettekoven H, Steerenberg PA, Kruizinga W, Van Noorle Jansen LM, Sekhuis J, Ruitenberg EJ

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Cancer Immunol Immunother; 12(1):21-29 1981

Two BCG preparations, one prepared by the usual method involving surface culture followed by homogenization (A) and the other consisting of dispersed culture (B), were compared. Both preparations caused initial decrease in both weight of Swiss mice. Serum glutamic transaminase increased in a comparable way when similar amounts of preparation of both BCG types were used, and spleen stimulation (by spleen index) was similarly affected by both. BCG-A produced an early and a late peak in stimulation of the popliteal lymph node, but BCG-B only caused a second peak. BCG-B with a suboptimal concentration of phytohemagglutinin (PHA) showed a synergistic stimulation of human lymphocytes in vitro, but similar BCG-A did not; minimal stimulation was observed with BCG of either type lacking PHA. Both preparations gave similar activation of NK cells and of macrophages (clearing Listeria monocytogenes). Retardation of the growth of murine fibrosarcoma tumors was evident when concentrations above 1 x 10(7) culturable particles of either BCG preparation were administered to female BALB/c mice; concentrations below that amount stimulated tumor growth. (34 Refs)

30. EARLY CHANGES IN THE RADIOSENSITIVITY OF CORYNEBACTERIUM PARVUM-STIMULATED CFU-S.

Maruyama Y, Grider C

Dept. Radiation Medicine, Univ. Kentucky Medical Center, Lexington, KY, 40536

Stem Cells; 1(2):81-96 1981

Corynebacterium parvum injected ip into C57BL mice induced a progression of hemopoietic CFU-S of C57BL mice from the resting state immediately after, and in the early period (approx 8 hr) after stimulation. Dose-response survival curves were determined for resting, 4 hr C parvum-stimulated, and then 'suicided' with high specific-activity tritiated thymidine (HSATT), and 6 hr cells exposed to vinblastine (VBL) and HSATT 1 hr before radiation. Dose-response survival curves of the stimulated endogenous spleen CFU-S after the injection revealed changing slopes or dose to reduce survival by 0.37 on the linear curve (D0) of dose-response curves indicative of changing sensitivity states. Shortly after stimulation with C parvum injection the sensitivity of cells indicated that they were in the DNA-S phase. D0 survival curve slope changes reflect radiosensitivity changes. Sensitivity increased shortly after injection, but at about 6 hr sensitivity to HSATT disappeared and the radiosensitivity increased. Sensitivity to VBL became evident at 7 hr with the begining of mitosis and mitotic sensitivity to VBL. A dose-response survival curve for the G2 phase CFU-S was determined using both HSATT and VBL to eliminate the DNA-S phase and mitotic cells. G2 sensitivity showed a complex bending dose-response curve with a terminal D0 of 58 rad. The D0 values indicate that D0 for resting endogenous CFU-S was 80 rad, for the DNA-S phase 105 rad, and for the late G1-early S phase 85 rad. The radiosensitivities were measured in vivo. CFU-S progression was blocked by metiamide the anti-histamine H2 receptor agent. (27 Refs)

31. DEPRESSION OF HEPATIC BIOTRANSFORMATIONS BY CHEMICAL IMMUNOADJUVANTS.

Giampietri A, Puccetti P, Contessa AR
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J Immunopharmacol; 3(2):251-264 1981

Two synthetic immunoadjuvants, pyran copolymer (PC) and polyinosinic-polycytidylic acid (polyI:C) were compared with Corynebacterium parvum and BCG in terms of their ability to depress the hepatic microsomal enzyme system (HMES) in hybrid mice. BCG, C parvum and PC had similar HMES-depressing effects as determined by aniline hydroxylase-aminopyrine demethylase assay. PolyI:C had a similar effect, but produced maximal response 1-3 days after administration, compared to 5-7 days for the other agents. Both polyI:C and PC were effective in a dose-dependent way. Macrophage activation in the spleen was assessed by growth inhibition of human myeloid cell line K-562; the PC-induced depression of the HMES paralleled that of macrophage activation, with peaks near 8 days of treatment for both. The possible relationship between macrophage functional activity and depression of hepatic biotransformation was studied by interfering with the reticuloendothelial system of mice with silica and whole-body irradiation (500 R). These treatments did not by themselves depress HMES activity; they did not reverse PC activity, but silica blocked C parvum activity. The present data suggest that immunoadjuvant depression of HMES is partially due to mononuclear phagocyte activity as well the presence of inflammatory lesions in liver parenchyma. (20 Refs)

CYTOKINE THERAPY

32. SPECIFIC CYTOTOXICITY AGAINST AUTOLOGOUS TUMOUR AND PROLIFERATIVE RESPONSES OF HUMAN LYMPHOCYTES GROWN IN INTERLEUKIN 2.

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Int J Cancer; 29(1):33-39 1982

Peripheral blood lymphocytes of cancer patients were sensitized in vitro to autologous tumor cells in mixed lymphocyte-tumor culture (MLTC). Blast cells were isolated on discontinuous Percoll gradients from MLTC which showed significant stimulation of [3H]-thymidine incorporation. Cultured T cells (CTC) were derived from these blasts by growth in conditioned medium containing interleukin-2 (IL-2) and maintained for up to 51 days by repeated feeding with IL-2 and in some cases by addition of irradiated allogeneic blood mononuclear cells as 'fillers.' These cultures showed specific cytotoxic reactivity against autologous tumor, and in only a few cases was natural killing (NK) of K562 cells apparent. Restimulation of CTC with tumor was measured in primed lymphocyte tests (PLT). Increased uptake of [3H]-thymidine was found upon stimulation by autologous tumor and allogeneic tumor of the same site and histology, but there was no response to non-related tumors or to a panel of allogeneic lymphocytes. No sensitization to autologous HLA D/DR could be detected by restimulation or cytotoxicity against monocytes in the majority of cases. These data suggest that, by careful selection of sensitized blasts from MLTC, it is possible to obtain CTC with both helper (proliferative) and cytotoxic T cells and that such CTC have specific reactivity against tumor cells. These cellular reagents will be useful in defining the antigenicity of human neoplasms and possibly in therapy. (Author abstract) (39 Refs)

33. INHIBITION OF NK ACTIVITY BY SUGARS: EFFECT OF INTERLEUKIN 2.

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Ann Immunol (Paris); 132(3):327-337 1981

Effects of sugars, particularly D-mannose (DM), on the natural killer (NK) activity of fresh peripheral blood lymphocytes from normal donors and of cultured T lymphocytes (CTC) activated in a mixed lymphocyte reaction and incubated in a conditioning medium (CM), containing phytohemagglutinin (PHA), beta-interferon, and interleukin 2, were examined. DM produced a dose-dependent, linear decrease in NK activity with a mean inhibition of 60% with 100 mM DM. Other sugars, including xylose and sucrose, also inhibited NK activity; no specificity for D or L forms was observed. DM-induced inhibition of NK activity occurred via the effector cells: only preincubation of effector cells with DM during the 2 hr prior to testing inhibited NK activity. Increased cytotoxicity resulted when target cells (K562 human chronic myeloid leukemia cells) were preincubated with DM. NK activity was increased by 40% after incubation of cells in mixed lymphocytes culture and then CM. These CTC were resistant to DM-induced inhibition of NK activity. Preincubation of lymphocytes with beta-interferon increased NK activity by 120%; this NK activity was inhibited by DM. Preincubation of lymphocytes with PHA produced no NK activity resistant to DM inhibition. The results suggested that DM inhibition of NK activity is mediated by interleukin 2 and not by CM or interferon. (14 Refs) (In FRE)

34. EFFECTS OF PARTIALLY PURIFIED INTERLEUKIN 2 IN VIVO ON LYMPHOCYTE POPULATIONS, CYTOTOXIC ACTIVITY TO TUMOUR CELLS AND SUPPRESSOR CELL ACTIVITY (MEETING ABSTRACT).

Hersey P, Bindon C, Edwards A, Bradley M, Murray E, McCarthy WH

No affiliation given

Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

The in vivo effect of interleukin 2 (IL2) was studied in patients with advanced melanoma. IL2 was prepared by stimulation of blood lymphocytes with phytohemagglutinin (PHA) for 24-36 hr and partially purified by membrane chromatography. The clearance rate (T1/2) of IL2 from the circulation was 22.5 min. Neutrophilia, lymphocytopenia and depletion of spontaneous cell mediated cytotoxicity (CMC), measured in 51 Cr release assays, were noted in the first few hr after injections. In the days following the injections of IL2, a number of changes were seen in blood leukocytes which included an increase in the percentage of E rosettes and fluctuations in CMC. The marked increase in CMC to allogeneic target cells seen after culture of lymphocytes in IL2 for 5-6 days was not seen in vivo. Instead reductions in CMC were observed at 2-3 and 8-9 days after the IL2 injections for periods lasting 2-7 days - the actual timing and duration of the reduction appeared autologous melanoma cells was seen 7 and 13 days after the injections and appeared to persist for 5-16 days depending on the dose of IL2. Suppressor activity measured in pokeweed mitogen stimulated cultures of B and T cells was in general raised after the IL2 injections but the timing of changes in the latter activity could be clearly related to changes in CMC. (no Refs)

35. T-CELL GROWTH FACTOR (INTERLEUKIN 2) CONTROL OF T-LYMPHOCYTE PROLIFERATION: POSSIBLE INVOLVEMENT IN LEUKEMOGENESIS.

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Transplant Proc; 13(4):1884-1890 1981

Isolation of murine and human leukemic T-cell lines that produce exceptionally high quantities of interleukin 2 (IL-2), and screening of freshly isolated patient-derived human leukemic blasts for IL-2 production and response capabilities, are described. An IL-2 microassay was used to screen fractions of biochemically manipulated, conditioned medium for the capacity to promote sustained in vitro proliferation of murine cytotoxic T-lymphocytes. Two leukemic cell lines, murine LBRM-33 and human Jurkat-FHCRC, produced large quantities of IL-2 upon stimulation with phytohemagglutinin (PHA). Both of the cell lines bear conventional T-cell markers and phenotypic markers indicative of immature cell type. Analysis of leukemic blast cell response of mononuclear blood cells from patients with various leukemias revealed consistent IL-2 production and response patterns. All patients who exhibited high levels of deoxynucleotidyl transferase (TdT) in leukemic blood cells showed a small proliferation increase in response to PHA stimulation but produced exceptionally high levels of IL-2. The response to added purified human IL-2 and PHA was atypical in most patients, in that incorporation of 3H-thymidine decreased in the majority of TdT+ leukemias when compared to PHA-stimulated proliferation. Such a finding was in marked contrast to results obtained with normal lymphocytes. IL-2 production and use responses and TdT expression in leukemic cells are discussed. (17 Refs)

36. LYSIS OF TUMOR BIOPSY CELLS BY AUTOLOGOUS T LYMPHOCYTES ACTIVATED IN MIXED CULTURES AND PROPAGATED WITH T CELL GROWTH FACTOR.

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J Exp Med; 155(1):83-95 1982

Lymphocytes of patients activated in mixed lymphocyte culture (MLC) lysed allogeneic third-party cells and in some cases also lysed autologous tumor cells. Allogeneic but not autologous phytohemagglutinin (PHA) blasts were also damaged by these effectors. The cytotoxic potential of MLC-activated lymphocytes from healthy donors was similar: allogeneic tumor and PHA blasts but not autologous PHA blasts were lysed. The cytotoxicity of lymphocytes activated in autologous tumor cells were specific for the stimulator because they acted only on the autologous tumor cells. Results obtained in cold target competition assays suggested that activated lymphocytes lyse the third party tumor targets because of alloantigen recognition and in MLC, several different sets of alloreactive cytotoxic lymphocytes are present simultaneously. There all-reactive cells are different to those that act on autologous tumor cells. The lysis of allogeneic tumor cells by lymphocytes of the patient is probably not due to recognition of cross-reacting tumor related antigens, and the antitumor cytotoxicity of the patients' MLC-activated lymphocytes is due to specifically reacting cells. (40 Refs)

37. THE ROLE OF IA IN T-CELL ACTIVATION.

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Transplant Proc; 13(4):1843-1845 1981

The role of IA region antigen in T-cell activation is discussed. Antigen-specific proliferation of primed T cells requires the presentation of antigen on histocompatible, IA-positive, adherent cells (APC). Recent advances in the field of interleukins suggest an alternate model in which the T cell recognizes antigen on the macrophage and activates the macrophage to produce IL1. T cells become activated after interaction with antigen and IL1 and develop receptors for IL2. Other T cells become activated and produce IL2, which has T-cell growth factor activity. The production of 'helper factor' is blocked by anti-Ia sera in a number of experimental models. Helper factor is a mixture of IL1, IL2, and a third factor, TRF. The production of IL1 is blocked by the presence of monoclonal anti-Ia; as a consequence of the block, no IL2 or TRF is produced. The production of IL2 can be restored by addition of IL1. The antigen stimulation of the IL2 producer cell does not require an IA-positive cell. Cultures of a long-term alloreactive T-cell line (C.C3.11.75) produce TRF factor. The line is specific for a private specificity of IAk and responds when stimulated with the antigen. The production of TRF in response to self + X must involve IA-restricted interaction with a macrophage or a B cell. Whether other T-cell interactions with antigen are IA restricted is not yet known. (7 Refs)

38. ESTABLISHMENT AND CHARACTERIZATION OF HUMAN T HYBRID CELLS SECRETING IMMUNOREGULATORY MOLECULES.

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Proc Natl Acad Sci USA; 78(12):7717-7721 1981

Hybridization of human T cells with an azaguanine-resistant human T cell line gave rise to T hybrid cell lines secreting several immunoregulatory molecules. Analyses of karyotypes, HLA phenotypes, and other surface phenotypes, such as T-cell-specific antigens or receptors for sheep erythrocytes and the patterns of mitogen responsiveness confirmed that the hypoxanthine/aminopterin/thymidine-resistant cell lines were human T-T hybridomas. One of the established hybrid clones (24-A) secreted human interleukin-2 (IL-2). The culture supernatants induced the proliferation of concanavalin A-stimulated murine T cells and supported the proliferation of an IL-2-dependent human cytotoxic T-cell line. In a clone (38-B) that did not show any IL-2 activity in culture supernatants, the addition of macrophages induced IL-2 production in the presence of phytohemagglutinin, suggesting that interleukin-1 induced IL-2 production in T hybrid cells. Hybrid cells secreting killer helper factor were also established. The culture supernatants from this clone, 55-A, helped the induction of cytotoxic T cells against UV-treated human B-blastoid cells but did not show any IL-2 activity. (Author abstract) (19 Refs)

39. MECHANISMS CONTROLLING TCGF PRODUCTION BY CLONED SUBLINES OF EL-4 AZGR IN RESPONSE TO STIMULATION BY ANTI-THY-1 ANTIBODY.

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J Immunol; 128(1):296-301 1982

The effect of xenogeneic anti-Thy-1 antibody on T cell growth factor (TCGF) production by T lymphoma cell lines has been examined as a model system for T cell activation. EL-4 G12 (a cloned subline of the producer EL-4 azgr cell line) produced TCGF when stimulated by a high concentration of anti-Thy-1, but none was induced by low concentrations of anti-Thy-1. Large amounts of TCGF were produced when these cells were cultured with Fc-receptor positive (FcR+) accessory cells. TCGF production by EL-4 G12 showed dose response kinetics similar to TCGF production by anti-Thy-1 stimulated purified normal spleen T cells. Goat anti-rabbit IgG (GaRIG) and Protein A substituted for this accessory helper effect, but neither FcR+ cells nor Protein A worked when (Fab')2 anti-Thy-1 was used instead of IgG anti-Thy-1. Anti-T-200 monoclonal antibody inhibited anti-Thy-1-induced TCGF production by EL-4 G12 and accessory cells. Phorbol myristic acetate and lymphocyte-activating factor also substituted in part for the accessory cell help. The data suggest there are at least two different accessory cell help mechanisms in anti-Thy-1-induced TCGF production, anti-Thy-1-bound membrane aggregation either by GaRIG, Protein A or FcR, and a LAF-dependent mechanism. (Author abstract) (29 Refs)

40. ACTIVATION OF FC RECEPTOR-BEARING LYMPHOCYTES BY IMMUNE COMPLEXES. II. KILLER LYMPHOCYTES MEDIATE FC LIGAND-INDUCED LYMPHOKINE PRODUCTION.

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J Exp Med; 154(6):1868-1880 1981

The roles of the constant fragment (Fc) portion of IgG (Fc gamma) and of the Fc gamma receptors (FcR) in immune complex-induced lymphokine production (ICLP) were studied. Nonadherent lymphocytes enriched 3-to 4-fold in killer (K) cells and in other Fc gamma-binding cells showed antibody-dependent cellular cytotoxicity (ADCC) at approx 1/10 of the lymphocyte:target ratios required for unfractionated nonadherent lymphocytes. These K-cell enriched lymphocytes were induced by chicken antibody-sensitized RBC (EA), by aggregated human gamma globulin (AgHGG), or by sensitized P815 mouse mastocytoma cells to produce lymphocyte migration-inhibiting factor (LIF) at approx 1/10 of the concentration necessary for production of similar levels of activity by unfractionated cells. K cell but not natural killer (NK) cell depletion virtually eliminated ADCC and ICLP. K cells incubated with antibody-sensitized glutaraldehyde-treated P815 cells produced high levels of LIF in the supernatant; NK cells yielded little or no LIF activity when incubated with or without AgHGG. Isolated Fc gamma fragments stimulated nonadherent lymphocytes to produce high levels of LIF activity. Fc gamma fragments did not inhibit WBC migration but blocked EA-rosette formation by lymphocytes. Binding of Fc gamma ligands to FcR of the appropriate lymphocytes was the only requirement for ICLP. (49 Refs)

41. MACROPHAGE ACTIVATION FOR TUMOR CYTOTOXICITY: CONTROL OF CYTOTOXIC ACTIVITY BY THE TIME INTERVAL EFFECTOR AND TARGET CELLS ARE EXPOSED TO LYMPHOKINES.

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Cell Immunol; 65(1):52-65 1981

Macrophages continuously exposed to lymphokines (LK) and target cells throughout a 48 hr cytotoxicity assay exhibit three-fold more tumoricidal activity than do cells optimally treated with LK before addition of tumor cells. Increased cytotoxic activity induced by continuous LK treatment was not due to direct toxic effects of LK on tumor target cells or to alterations in target cell susceptibility to cytopathic effects of LK-activated macrophages. Moreover, sensitivities of responsive macrophages to LK activation signals and time courses for onset and loss of tumoricidal activity during continuous exposure or LK pulse were identical. Analysis of macrophage or LK dose responses and time courses of development of cytotoxicity each suggest that differences in tumoricidal activity between macrophages continuously exposed or pulsed with LK were quantitative: the number of cytotoxic events was increased 2.7 +-0.2-fold (mean +- SEM for 11 experiments) during continuous LK treatment. Optimal levels of macrophage tumoricidal activity then occur only if effector cells, target cells and activation stimuli are simultaneously present for a defined time interval: tumor cells need not be present during the initial 2 or 3 hr of culture; LK can be removed after 8 hr with little or no loss of cytotoxic activity. However, removal of LK or target cells during the critical 4-to 8-hr interval decreased levels of cytotoxicity three-fold. Thus, nonspecific effector function by LK-activated macrophages is controlled by both the physicochemical nature of the LK mediator and the time interval effector and target cells are exposed to LK. (Author abstract) (20 Refs)

42. INCREASED RESPONSES TO LYMPHOKINES ARE CORRELATED WITH PRELEUKEMIA IN MICE INOCULATED WITH MOLONEY LEUKEMIA VIRUS.

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Proc Natl Acad Sci USA; 78(12):7712-7716 1981

In various mouse strains, inoculation with Moloney leukemia virus results in the establishment of an acute viremia which in most cases is followed by the induction of leukemia. Also associated with the viremia is the development of a chronic cellular immune response detectable in vitro by the ability of viral proteins to induce splenic lymphocyte proliferation. Previous studies have demonstrated that, in the absence of this cellular immune response, leukemia does not develop irrespective of whether viremia is present. In vitro proliferative responses to antigens involve the nonspecific response of various subpopulations of lymphocytes to lymphokines produced by antigen-specific Thy 1+, Lyt 1+,2-lymphocytes. The studies presented here concern the effects of a chronic immune response in viremic mice on the frequency of lymphocytes capable of responding to lymphokines in vitro. The data demonstrate that the number of responsive lymphocytes is increased 30-to 100-fold in preleukemic mice and that such increases are dependent upon the induction of an immune response in viremic mice. The role of this altered immune response in leukemia is discussed. (Author abstract) (18 Refs)

43. ENHANCEMENT BY IMMUNOSTIMULANTS OF THE PRODUCTION BY MOUSE SPLEEN CELLS OF FACTOR(S) STIMULATING DIFFERENTIATION OF MOUSE MYELOID LEUKEMIC CELLS.

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Gan; 72(6):828-833 1981

Mouse myeloid leukemic Ml cells can be induced to differentiate into macrophages and granulocytes in vitro by a factor(s) stimulating differentiation of the cells (D-factor) or by various chemical compounds. Spleen lymphocytes and spleen macrophages have been shown to produce D-factor when treated with various mitogens including lipopolysaccharide or synthetic double-stranded polyribonucleotide, poly(I).poly(C). Several immunostimulants from microorganisms were tested for ability to induce differentiation of Ml cells and to stimulate production of D-factor by spleen cells. Mycobacterium bovis BCG (500 u g/ml) and the cell wall skeleton of Nocardia rubra (50 ug/ml) induced differentiation of Ml cells, but Corynebacterium parvum CN6134 and the cell wall skeleton of Propionibacterium acnes C7 had no effect on Ml cells. On the other hand, all immunostimulants tested at concentrations of more than 10 ug/ml were found to stimulate production of D-factor by both spleen lymphocytes and spleen macrophages. Synthetic derivatives of N-acetylmuramyl dipeptide (MDP), the minimal adjuvant-active subunit of the bacterial cell wall, had no direct effect on the differentiation of Ml cells and only slightly stimulated the production of D-factor by spleen cells. Therefore, the structure of microorganisms required for induction of differentiation of Ml cells and for stimulation of production of D-factor are suggested to be different from that of MDP. (Author abstract) (27 Refs)

THYMIC HORMONES AND OTHER IMMUNORESTORATIVE AGENTS

44. THE EFFECT OF THYMUS EXTRACT ON CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) AND NORMAL LYMPHOCYTES ASSESSED BY LOCAL XENOGENEIC GRAFT VERSUS HOST (GVH) REACTION (MEETING ABSTRACT).

Burek B, Hauptmann E, Jaksic B, Vitale B
Department of Experimental Biology and Medicine, 'Rudjer Boskovic' Institute, Zagreb, Yugoslavia
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

The functional reactivity of lymphocytes from healthy subjects and patients with CLL was assessed by local GVH reaction in rats. On day 6 after intradermal (i/d) injection of human lymphocytes in previously immunosupressed rats, the Evans blue was iv injected and the diameter of blue spot in the skin was measured. It was found that functional reactivity of lymphocytes in patients with CLL was depressed in comparison with the reactivity of lymphocytes in healthy subjects. The in vitro incubation of lymphocytes with soluble thymus extract could enhance (in normal subjects) or restore (in CLL patients) id GVH reaction in rats. This effect depended on the number of inoculated cells and concentration of thymus extract. The ability of thymus extract to restore functional reactivity of lymphocytes obtained from CLL patients further depended upon the clinical stage of the disease. In nonprogressive (stable) phase of CLL, restoration of the functional reactivity of lymphocytes was still possible, while in progressive (unstable) phase of CLL, restoration could not be achieved. In conclusion, the intensity of local GVH reaction in rats provoked by id injection of lymphocytes from CLL patients previously incubated with thymus extract, could serve as an additional functional parameter of the disease. (no Refs)

45. CHANGES IN THYMUS FACTOR LEVEL IN RATS WITH JENSEN SARCOMA AND THE INFLUENCE OF APPLICATION OF THYMUS HORMONE ON TUMOR GROWTH RATE.

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Z Exp Chir; 14(5):306-309 1981

Changes in the plasma levels of thymus factor (TF) and the effects of various treatments were studied in Wistar rats bearing transplanted Jensen sarcomas. Adult rats (90-110 g) were injected in the thigh with 10(8) tumor cells. TF levels were determined 16 days after transplantation (TP). The following treatments were used singly or in various combinations: (1) Local irradiation (RT) was begun 2 days after TP with a total dose of 21 Gray (3 Gray/day for 5 days, 2 days pause, and 3 Grays/day for 2 days). (2) Cyclic AMP levels were raised by ip injection of l-dihydroxyphenylalanine (l-DOPA: 100 mg/kg, 3 x/day for 6 days, followed by 1 x or 2 x/day for 6 days). (3) Interferon production was induced by injection of measles vaccine (MV: 10,000 TCD50/day im on days 1, 3, and 5 after TP). (4) TF was injected ip (0.2 ml 2 x/day, for 12 days, beginning 1 day after TP). The lowest rate of tumor growth was obtained with a combination of RT, l-DOPA, and MV (11/13 rats tumor-free). All tumor-bearing animals showed lower plasma TF levels (107-119 units) than tumor-free animals (188-239 units). Animals responding to treatment had TF levels comparable to untreated, tumor-free controls. TF treatment alone and a combination of l-DOPA and MV reduced tumor growth significantly. (20 Refs) (In GER)

46. IMMUNOCHEMICAL STUDIES ON THYMOSIN: RADIOIMMUNOASSAY OF THYMOSIN ALPHA1.

McClure JE, Lameris N, Wara DW, Goldstein AL
Dept. Biochemistry, George Washington Univ. Sch. Medicine and Health Sciences, Washington, DC, 20037
J Immunol; 128(1):368-375 1982

A sensitive and specific radioimmunoassay (RIA) has been developed to measure thymosin alpha1 in human blood and tissue extracts. Thymosin alpha1, originally isolated from bovine thymosin fraction 5, has an identical primary structure in bovine and human species. Antiserum to synthetic thymosin alpha1 was prepared in rabbits. A synthetic analogue, N-Ac-(Tyr(1))thymosin alpha1 was radioiodinated by utilizing Na125I and soluble lactoperoxidase. The RIA is capable of detecting as small an amount as 40 pg thymosin alpha1 in serum/plasma and does not significantly cross-react with other putative thymic hormones or other purified blood proteins that have been assayed. Proteolytic degradation of thymosin alpha1 does not occur during the collection, storage, or assay of serum or plasma. The concentration of thymosin alpha1 in the blood is highest in utero, decreases sharply after birth, and appears to remain fairly constant during the first 15 yr of life. Maternal blood levels of thymosin alpha1 appear to be above normal during pregnancy. (Author abstract) (28 Refs)

ACTIVE SPECIFIC IMMUNIZATION

47. IMMUNIZATION OF SYNGENEIC MICE AGAINST MALIGNANT MELANOMA WITH SUBCELLULAR MEMBRANE FRACTIONS OF A BROMODEOXYURIDINE-GROWN VARIANT.

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Cancer Immunol Immunother; 12(1):63-70 1981

In vivo tumor rejection activity (without adjuvant) of subcellular membrane fractions (CM) isolated from a non-tumorigenic mouse melanoma variant was examined. The C3471 variant line originated by continuous growth of tumorigenic B559 line in the presence of thymidine analog 5-bromodeoxyuridine. Immunization with CM from C3471 cells provided effective prophylaxis against formation of lethal B559 melanomas in challenged C57BL/6 mice; plasma membrane vesicles also provided immunization. Immunization with intact C3741 cells yielded more efficient rejection of B559 melanoma than did immunization with CM. CM of B559 cells were not immunogenic, although the latency period was approx doubled compared to controls. Normal intact, viable primary fascia cells and membranes from C57BL/6 mice had no immunogenic value. Mice immunized with intact C3471 cells could reject challenge by either in vivo-tumor derived or cultured B559 cells. Inoculation of spleen cells and peritoneal exudate cells from C3471 CM-immunized mice in Winn assays neutralized malignant properties of B559 melanoma cells in a dose-responsive way, indicating that the syngeneic host response elicited by CM of C3471 cells is cell-mediated. (44 Refs)

48. CELLULAR INTERACTIONS MODULATING HOST RESISTANCE TO TUMOURS.

Baldwin RW, Byers VS, Hannant D, Jones JA, Pimm MV, Price MR

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Recent Results Cancer Res; 80:338-345 1982

Active specific immunotherapy of carcinogen-induced rat tumors can be effected using vaccines containing tumor cells admixed with bacterial vaccines such as BCG and C parvum. The nature of the tumor antigen preparation is important, the most effective immunogen being viable tumor cells whose growth is controlled by responses generated by the bacterial agent in the vaccine. Soluble tumor antigen preparations are usually ineffective due to the preferential induction of suppressor lymphocyte responses in normal hosts. In comparison, removal of suppressor precursors by cyclophosphamide treatment of animals leads to the development of tumor immunity following immunization with soluble antigen preparations. One component of the immune rejection response involves the generation of non-specific effector cells. This type of response can also be induced by administering chemical hypersensitizing agents so as to localize tumor deposits. This approach has proved highly effective in treating the guinea pig line 10 hepatoma by intralesional injection of alkylcatechols. These compounds are highly potent hypersensitizers, being the active constituents of the poison ivy/oak (urushiol oil), and localize in tumor cell membranes. (Author abstract) (17 Refs)

ADOPTIVE IMMUNIZATION AND RELATED APPROACHES

49. ALLOIMMUNIZATION AND ADOPTIVE IMMUNOTHERAPY OF LEUKEMIA.

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Transplant Proc; 13(4):1910-1914 1981

Factors that affect induction of graft-vs-leukemia (GVL) reactivity (against AKR-L) in alloimmunized CBA/J mouse donors are described. Spleen cells from unimmunized or isoimmunized CBA donors had no GVL reactivity; 178/179 AKR secondary recipients died of leukemia within 90 days. CBA donors that were alloimmunized with viable lymphoid cells from H-2-compatible or -incompatible mice exhibited high levels of GVL reactivity. Immunization with lymphoid cells from H-2-compatible mice induced significantly higher levels of GVL reactivity than did lymphoid cells from H-2-incompatible mice. Irradiation of AKR-L or lymphoid cells from H-2-compatible donors significantly reduced the GVL reactivity induced in CBA donors in comparison with unirradiated cells. Heat treatment of alloimmunizing cells also significantly impaired induction of GVL reactivity. Inactivation of lymphoid cells with mitomycin C caused no significant reduction in their ability to induce GVL reactivity. Significant GVL reactivity was observed after alloimmunization with purified C3H/He (H-2k) epidermal cells but not with BALB/c (H-2d) cells. Antigens and mechanisms involved in GVL reactivity are discussed. (21 Refs)

50. ALIEN-DRIVEN DIVERSITY AND ALIEN-SELECTED ESCAPE: A RATIONALE FOR ALLOGENEIC CANCER IMMUNOTHERAPY.

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Transplant Proc; 13(4):1915-1921 1981

We have presented two theories relating to the function of histocompatibility antigens and their presence as alien antigens on tumor cells. The theory of alien-driven diversity suggests that the ability to effectively recognize pathogens in the form of 'altered-self' derives from prior exposure to antigens cross-reactive with 'altered-self' during development. Furthermore, these cross-reactive antigens are alloantigens that are expressed on autologous cells during somatic development. These somatically generated alloantigens could be the result of the same genetic alterations that produced the polymorphism of these antigens within the species. Second, the theory of alien-selected escape suggest that a tumorigenic pathogen selects a cell bearing an alien H* antigen so that the alien-infected cell is recognized as sel f rather than altered-self by the tumor host. We then summarized data from mouse and man consistent with these theories and with the concept that clinically evident tumors have escaped the host's immune system. Finally, we have discussed potential directions for devising immunotherapy with allogeneic cells that might circumvent the apparent unresponsiveness of the patient's immune system to his own tumor. (Author abstract) (20 Refs)

51. INHIBITION OF THE YC8 LYMPHOMA GROWTH BY ALLOIMMUNIZATION WITH NORMAL CELLS.

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Transplant Proc; 13(4):1906-1909 1981

Effects of alloimmunization with normal mouse lymphoid cells were studied in relation to the resistance of BALB/c mice to the growth of syngeneic Moloney virus-induced lymphoma YC8, previously shown to lack detectable amounts of alien H-2 antigens. Alloimmunization of BALB/c mice with normal lymphoid cells elicited a strong resistance to otherwise lethal doses of YC8 cells; the phenomenon was particularly evident and reproducible in mice immunized either with B10.A, B10.D2, or pool 5 lymphoid cells. Neither H-2 differences nor route of immunization affected the response. Alloimmunization with tissues of a single strain were less effective in reducing the growth of other syngeneic lymphomas and sarcomas. However, pool immunization with tissues of five different strains significantly retarded the growth of the BALB/c radiation-induced lymphoma RL(male)1, and of the urethan-induced BALB/c lymphoma Ur-1. The presence of effectors capable of killing YC8 cells in alloimmune BALB/c mice was examined in vitro. Efficacy of B10.D2 or DBA/2 but not of B10.A immunization in inducing anti-YC8 effectors indicated that in vivo and in vitro systems may have different requirements for the immune response. Immunity to YC8 was restricted by gene products of the major histocompatibility complex, possibly the Kd-IEd regions, in only the in vitro environment. The mechanism by which alloimmune prevention operates may involve a cross-reaction between antigens of normal allogeneic lymphocytes and antigens expressed by the tumor, natural killer-like cells, viral antigens, or alloreactivity. (14 Refs)

52. IMMUNOTHERAPY OF A MURINE COLON CANCER WITH SYNGENEIC SPLEEN CELLS, IMMUNE RNA AND TUMOR ANTIGEN.

Fukushima M, Colmerauer ME, Nayak SK, Koziol JA, Pilch YH
1st Dept. Surgery, Hirosaki Univ. Sch. Medicine, Hirosaki, Japan
Int J Cancer; 29(1):107-112 1982

In combination with xenogeneic immune RNA (I-RNA) and tumor antigen (TA), syngeneic spleen cells inhibited the growth of a N-methyl-N-nitrosourethane-induced colon carcinoma (CT-26) in BALB/c mice. The sequential administration of 1 x 10(7) spleen cells, 1 mg of anti-CT-26 I-RNA and 0.4 mg of CT-26 TA resulted in a 20% survival rate of mice bearing established CT-26 tumors. On the other hand, administration of the spleen cells only, I-RNA only or TA only was not effective in inhibiting tumor growth. Similarly, when any one of the three agents (I-RNA, TA and spleen cells) was omitted, no anti-tumor effect was obtained. A higher dose (1 x 10(8)) and a lower dose (1 x 10(6)) of spleen cells decreased the antitumor effect of this combination therapy. A higher dose (2 mg) and a lower dose (0.5 mg) of I-RNA, as well as a higher dose of TA (0.8 mg) had no influence on the antitumor effect. However, a lower dose of TA (0.2 mg) in combination with spleen cells and I-RNA decreased the antitumor effect. When all three agents were administered at higher or lower doses, no antitumor effect was obtained. When mice bearing CT-26 tumors were treated with spleen cells, plus I-RNA directed against a syngeneic but antigenically different tumor (BP/B/5) and BP/B/5 TA, with spleen cells plus CT-26 I-RNA and BP/B/5 TA, or with spleen cells plus BP/B/5 I-RNA and CT-26 TA, no antitumor effect was observed. These results indicate that the antitumor responses observed were due to tumor-specific immune responses. In conclusion, in order to obtain growth retardation or regression of established CT-26 tumor transplants, the sequential administration of all three agents (spleen cells, I-RNA and TA) was required. The optimal doses of each agent were found to be 1 x 10(7) spleen cells, 0.5 mg or 1 mg of I-RNA and 0.4 mg of tumor antigen. Higher or lower doses decreased the antitumor effect. Tumor-specific immune reactions appeared to be involved. (Author abstract) (21 Refs)

53. ANTI-TUMOR EFFECT OF SYNGENEIC SPLEEN CELLS TREATED WITH IMMUNE RNA AND TUMOR ANTIGEN.

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Int J Cancer; 29(1):113-117 1982

The antitumor effect of syngeneic spleen cells, xenogeneic immune RNA (I-RNA) and tumor antigen (TA) was studied in a chemically induced (N-methyl-N-nitrosourethane) colon carcinoma model in BALB/c mice. When the mice were treated, sequentially, with these three elements by local injection under the tumor, complete tumor regression was observed in 25% of the animals. Complete tumor regression was observed in 17% of animals treated by injection of spleen cells pre-incubated with I-RNA in vitro followed by an injection of TA. When spleen cells were treated first with I-RNA and then with mitomycin-C, therapeutic benefit was obtained and the survival rate of mice treated with these spleen cells and TA was significantly higher than that of the control group (no treatment). The antitumor effect of this treatment was abrogated completely when spleen cells were treated with mitomycin-C prior to I-RNA incubation. When spleen cells were incubated with TA in vitro or after incubation with I-RNA and then injected into tumor-bearing mice, no antitumor effect was noted. These data suggest that DNA synthesis and/or lymphocyte proliferation is essential for the action of I-RNA in sensitizing lymphocytes but not essential in the interaction of I-RNA-sensitized lymphocytes with TA. In addition it appeared that, under the conditions used, the participation of host factors was essential in the latter interaction, since treatment of I-RNA-sensitized lymphocytes with TA in vitro was ineffective. (Author abstract) (13 Refs)

54. MODULATION OF NATURAL CYTOTOXICITY BY ALLOANTIBODIES. V. THE MECHANISM OF A SELECTIVE AUGMENTING EFFECT OF ANTI-H-2 ANTISERA ON THE NATURAL KILLER ACTIVITY OF MOUSE SPLEEN CELLS.

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Cell Immunol; 65(1):115-130 1981

Treatment of mouse spleen cells with specific anti-H-2 antisera augments their natural killer (NK) activity against K562 cells but not against YAC target tumor cells. The same population of natural killer cells was found to lyse K562 as well as YAC target cells, since (a) depletion of YAC reactive NK cells by absorption on YAC monolayers resulted in a concomitant depletion of anti-K562 NK activity of mouse spleen cells, and (b) both K562 and YAC cells could inhibit their own as well as each others lysis in a cross-competition assay. Anti-H-2 antiserum could not induce anti-K562 NK activity in spleen cells previously depleted of NK cells by absorption on YAC monolayers, indicating that alloantiserum does not act by recruiting otherwise nonreactive cells to become cytotoxic toward K562 target cells. In a target-binding assay, K562 binding of NK cells (T-cell, B-cell-, and macrophage-depleted spleen cells) increased five- to eightfold in the presence of anti-H-2 antiserum whereas YAC cells binding of NK cells was not increased. H-2 antigens per se did not appear to be involved in the alloantisera effect since anti-NK antiserum directed against a non-H-2 antigen selectively expressed on NK cells, showed a similar selective NK enhancing effect. Protein A, a reagent which binds to the Fc region of immunoglobulin molecules, completely blocked the alloantiserum induced augmentation of anti-K562 NK activity, but did not alter basal NK activity. Moreover, the F(ab)2 fraction of alloantibodies failed to enhance anti-K562 cytotoxic activity of mouse spleen cells, indicating a crucial role for the Fc portion of the alloantibodies attached to the NK cells, in NK augmentation. Utilization of several target cell lines with or without membrane Fc receptors (FcR) revealed that alloantiserum enhanced the lysis of only FcR+ target cells. It is proposed that alloantibody-coated NK cells, as a result of a secondary interaction between attached alloantibody and Fc receptors on target cells, interact more readily with the target cells and thereby cause a higher level of lytic activity. (Author abstract) (25 Refs)

55. FUNCTIONAL PROPERTIES OF CONTINUOUSLY CULTURED HUMAN T LYMPHOCYTES.

Boylston AW, Anderson RL, Haworth CA
Dept. Experimental Pathology, St. Mary's Hosp. Medical Sch., London W2 1PG, England
Clin Exp Immunol; 43(2):329-335 1981

Properties of human T lymphocytes (CCTC) maintained in continuous culture by a new method were studied. CCTC did not proliferate in response to phytohemagglutinin, concanavalin A, or allogeneic lymphocytes. CCTC inhibited proliferation of normal cells in mixed lymphocyte culture and were cytotoxic to a number of human lymphoid cell lines. Properties of CCTC differed significantly from those of cells grown on T-cell growth factor. (16 Refs)

56. ESTABLISHMENT OF HUMAN T LYMPHOCYTE CLONES HIGHLY CYTOTOXIC FOR AN EBV-TRANSFORMED B CELL LINE IN SERUM-FREE MEDIUM: ISOLATION OF CLONES THAT DIFFER IN PHENOTYPE AND SPECIFICITY.

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J Immunol; 128(1):95-99 1982

A human T cell culture (HLA A2; w23 B40; W44 Cw4) was established by repetitive stimulation with an Epstein Barr virus-transformed B cell line JY in a serum-free culture medium. This T cell culture was highly cytotoxic for JY but had negligible nonspecific natural killer cell-like activity against the myeloid cell line K562. Cloning by limiting dilution procedures in serum-free medium resulted in a high plating efficiency and the establishment of a large number of cytotoxic clones. Three of these clones (31, 38, and 77) were selected. Phenotypic characterization by using a series of monoclonal antibodies and fluorescein isothiocyanate-labeled goat anti-mouse immunoglobulin revealed that clone 31 was OKT 3+, 4-, T8+, Ia+, OKM 1-, whereas clone 38 was OKT 3+, 4+, T8-, Ia+, and OKM 1-, indicating that cytotoxic T cells are not restricted to the T8+ subset and can reside in the OKT 4+ 'inducer/helper' T cell subset. Because the cytotoxic reaction of clone 31 was inhibited by a monoclonal antiserum that recognizes all HLA A, B, and C specificities, whereas that of clone 38 was not blocked, it was concluded that in contrast to clone 38, clone 31 recognized HLA A, B, or C antigens. A preliminary analysis indicated that clone 31 reacted with HLA B7. The specificity of clone 38 remained unclear. The cytotoxic reaction of the T8+ clone 31 was blocked by anti-T8, a monoclonal antibody specific for human cytotoxic/suppressor T cells, suggesting that the T8 determinant plays a role in the cytotoxic process. The cytotoxic reaction of the T8-clone 38 was not blocked by anti-T8. The third clone (77), which was OKT 3+, 4-, T8+, Ia+, and OKM 1-, was cytotoxic only in the presence of minimal concentrations of lectin. Our results indicate that stable cytotoxic T cell clones can be established successfully in serum-free medium. (Author abstract) (26 Refs)

57. CHARACTERIZATION OF ALLOANTIGEN-ACTIVATED HUMAN LYMPHOCYTES CYTOTOXIC FOR AUTOLOGOUS EB VIRUS-TRANSFORMED LYMPHOBLASTOID CELL LINES.

Zarling JM, Ferrone S, Bach FH, Gillis S, Meruelo D, Martin WJ
Immunology Res. Center, Dept. Lab. Medicine/Pathology, Univ. Minnesota, Minneapolis, MN, 55455
Transplant Proc; 13(4):1893-1896 1981

Previously reported results on the ability of cytotoxic T lymphocytes (Tc) or natural killer (NK)-like cells to mediate lysis of autologous Epstein-Barr virus-transformed lymphoblastoid cell lines (LCL) by lymphocytes stimulated with pooled allogeneic normal cells are summarized. Studies of the effect of 5-bromodeoxyuridine and light on generation of cytotoxic cells capable of lysing autologous LCL cells indicated that alloantigen-induced effector cells that lyse autologous LCL cells are similar to those lysing allogeneic normal cells. Treatment of fresh lymphocytes with monoclonal antibody OKT3 (reactive with greater than 95% of RBC-rosetting cells) or OKT8 (reactive with a subpopulation of T cells) and complement (C') did not reduce NK activity against K562 leukemia cells. Treatment of fresh lymphocytes with monoclonal antibody OKM1 (reactive with macrophages and a small proportion of nonadherent cells) and C' decreased NK cell activity by approx 75%. Thus the majority of NK cells appear to be OKT3-, OKT8-, OKM1+. The phenotype of mixed WBC culture (MLC)-generated cells that lyse autologous LCL was the same as that of Tc which lyse allogeneic normal cells (OKT3+, OKT8+); NK-like cells generated in MLC, which lyse K562 cells, were OKT3-, OKT8-. The results indicate that lysis of autologous LCL cells by pool-stimulated cells is mediated by Tc. (16 Refs)

SEROTHERAPY AND RELATED APPROACHES

58. SPECIFIC KILLING OF A HUMAN BREAST CARCINOMA CELL LINE BY A MONOCLONAL ANTIBODY COUPLED TO THE A-CHAIN OF RICIN.

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Cancer Immunol Immunother; 12(1):39-41 1981

The H59 hybridoma antibody, an IgMk antibody specific to a subset of human breast carcinoma cells, was coupled with the isolated A-chain of ricin. The resulting hybrid molecule retained both antibody binding activity and A-chain toxic activity against ZR75-1 and MCF-7 breast cancer cell lines. Results show that the principle of antibody toxin targeting to nonlymphoid tumor can be extended to include a human breast carcinoma. (14 Refs)

59. MONOCLONAL ANTIBODY SPECIFIC FOR HUMAN T ACUTE LYMPHOBLASTIC LEUKEMIA.

Deng CT, Chia J, Terasaki P, Billing R
Dept. Surgery, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Lancet; 1(8262):10-11 1982

A cytotoxic mouse monoclonal antibody (CALL2) was produced against a cultured T acute lymphocytic leukemia (T ALL) cell line 8402. Ascites fluid containing the antibody was cytotoxic to a titer of up to 1:100,000 against four of six cultured T ALL cell lines and against leukemia cells from seven of eight T ALL patients and one of five T chronic lymphatic leukemia patients. The antibody did not react with normal peripheral-blood T and B lymphocytes, monocytes, granulocytes, spleen cells, thymocytes, platelets, and other acute and chronic leukemia cells. The CALL2 antibody did not react with bone marrow stem cells of the myeloid series (CFU-C). This antibody may be useful for passive immunotherapy trials since it does not react with normal cells and is highly cytotoxic to T ALL cells. (Author abstract) (9 Refs)

60. MONOCLONAL ANTIBODY-RICIN A CHAIN CONJUGATE SELECTIVELY CYTOTOXIC FOR CELLS BEARING THE COMMON ACUTE LYMPHOBLASTIC LEUKEMIA ANTIGEN.

Raso V, Ritz J, Basala M, Schlossman SF
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Cancer Res; 42(2):457-464 1982

The toxic subunit of ricin has been conjugated by a disulfide bone to a monoclonal murine antibody (J-5) specific for the common acute lymphoblastic leukemia antigen (CALLA) expressed on human lymphoblastic leukemia cells. Both the monoclonal antibody and ricin A chain retained their original biological activity after conjugation. The ricin A chain antibody-combining site attached to the membrane of CALLA-bearing cells, whereupon both components of the molecule, antibody and A chain, could be detected using fluorescein-labeled antibody probes directed against either mouse F(ab')2 or ricin A chain. This conjugate proved to be a potent cytotoxin for CALLA-positive Nalm-1 cells growing in vitro and produced 50% inhibition of proliferation at levels of 2 x 10(-10) M. CALLA-negative cell lines were unaffected until levels of conjugate approached 10-6 M. When tested for cytotoxic action on Nalm-1 cells, the composite conjugate molecule was at least 2,000x more effective than J-5 antibody alone, ricin A chain alone, or a noncovalent mixture of these components. Cytotoxicity of the conjugate could be blocked completely by addition of antibodies specific for either mouse Ig or ricin A chain. Direct comparison of the in vitro cytotoxity of CALLA-directed univalent Fab versus bivalent F(ab')2 carriers of ricin A chain revealed 70-fold greater efficacy for the latter conjugate. This differential could not be accounted for by differences in A chain activity or binding affinity for the cell membrane but appeared related to the ability of the multivalent agent to induce modulation and internalization of CALLA determinants. No overt toxic effects were noted when the F(ab')2-A chain conjugates was administered iv to rabbits at levels as high as 20 mg/kg single injection or 5 mg/kg for 5 days. The unique specificity characteristics and high potency of this cytotoxic conjugate indicate that it has significant therapeutic potential for the treatment of CALLA-bearing human leukemias and lymphomas. (37 Refs)

61. BIOCHEMICAL AND IMMUNOLOGIC HETEROGENEITY OF IA GLYCOPROTEINS ISOLATED FROM A CHRONIC LYMPHOCYTIC LEUKEMIA.

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J Immunol; 128(1):217-223 1982

Ia glycoproteins have been isolated from human chronic lymphocytic leukemic cells (CLL) by Lens culinaris chromatography and by filtration on ACA-34 Ultrogel. Ia antigenic activity, measured by inhibition of the cellular radioimmunoassay, was separated by gel filtration into two fractions, Peak I and Peak II. Monoclonal antibodies, produced against Peak II glycoproteins, appear to recognize different antigenic determinants of Ia molecules. Monoclonal antibody 18a4 reacted with Ia molecules of Peaks I and II, whereas monoclonal antibodies 18c2 and 18d5 reacted almost exclusively with Peak II molecules both in the cellular radioimmunoassay and by immunoprecipitation. In addition to antigenic differences, minor variations in the apparent mol wt of the Ia polypeptide chains were observed between Peaks I and II. These results indicate the existence of antigenically distinct subsets of Ia molecules that are separable by gel filtration. (Author abstract) (50 Refs)

62. DETECTION OF THE HUMAN T CELL LYMPHOMA VIRUS P19 IN CELLS OF SOME PATIENTS WITH CUTANEOUS T CELL LYMPHOMA AND LEUKEMIA USING A MONOCLONAL ANTIBODY.

Robert-Guroff M, Ruscetti FW, Posner LE, Poiesz BJ, Gallo RC

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J Exp Med; 154(6):1957-1964 1981

The p19 monoclonal antibody for human T cell lymphoma virus (HTLV) and expression of HTLV p19 in cells of patients with leukemia and lymphoma are described. Radioimmune precipitation assay for HTLV proteins demonstrated the specificity of the antibody. Among the iodinated HTLV proteins, only p19 could be specifically precipitated. In indirect immune fluorescence assays, anti-p19 specifically labeled only HTLV-producing cells. Transformed HUT78 cells, derived from a patient with either cutaneous T cell lymphoma or leukemia (CTLC), did not produce HTLV and were negative for p19. Both HUT102 parental cells and clones were 60-70% positive, suggesting that viral expression might be related to cell cycling. CTCL-2 and CTCL-3 cells were 5% and 12% positive, respectively. The fluorescent labeling of virus-positive cells was restricted to the cell membrane. Only fixed cells were labeled, supporting the idea that p19 is an internal HTLV protein and not an envelope component. HTLV p19 is not expressed in most malignant T cells, indicating that replicating HTLV is not present. The monoclonal antibody to HTLV p19 provides an assay of HTLV expression for determining the frequency of HTLV replication in human T cells and for studying the regulation of viral gene expression. (14 Refs)

63. MONOCLONAL ANTIBODIES AGAINST SURFACE ANTIGENS OF LARYNGEAL CARCINOMA CELLS.

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Arch Otorhinolaryngol; 233(2):161-172 1981

Production of monoclonal antibodies against laryngeal carcinoma (LC) cells is reported. BALB/c mice were immunized with LC cells of line HLaC78 (1 x 10(6)-5 x 10(7) cells x 2 at a 6-wk interval) or with cell membranes (CM) from LC cells. Spleen cells were obtained 3 days after the second injection. Spleen cells were fused with mouse myeloma 653 cells to form antibody-producing cells capable of proliferation. A total of 1,882 clones of spleen cells were developed, including 1,102 from mice immunized with CM and 780 from mice immunized with intact cells (IC). Antibodies that bound to intact LC were produced by 73 clones, all from IC-immunized mice. Antibody from one clone was identified which bound malignant target cells, including two types of LC and two types of salivary gland tumor cells, but which did not bind normal fibrocytes, lymphocytes, or other normal human cell types, or nonhuman cells. The antibody, produced by hybridoma clone 1g6, was an IgG. Diagnostic potential of the IgG is described. (32 Refs) (In GER)

64. HYBRIDOMA MONOCLONAL ANTIBODY: USE IN DEFINING SURFACE ANTIGENS ON HUMAN LUNG CARCINOMA CELLS.

Kasai M, Saxton RE, Holmes EC, Burk MW, Morton DL, Bonnard, Alexander P, Ferrone S, Ivanyi P, Nathanson SD, Pious D, Embleton MJ

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Transplant Proc; 13(4):1942-1946 1981

Surface antigens on UCLA-SO-P3, the squamous cell lung carcinoma cell line derived from a 53-yr-old man, were compared with those on PL3, the autologous lymphoblast line obtained from the same patient. Using the autologous cell lines, two hybridomas were selected which secrete monoclonal antibodies that bind antigenic determinants present at high density on the carcinoma cells but not on the paired lymphoblastoid cells. The two cloned hybridomas, designated 169D4 and 169F3, were grown as ascites tumors in mineral oil-primed BALB/c mice. The two binding curves obtained by titration of hybridoma cells with P3 and PL3 target cells were compared. An end-point titer greater than 1:100,000 for both antibodies to the P3 carcinoma but only 1/:10 to PL3 for the 169D4 monoclonal antibody and 1:100 for 169F3 was revealed. The shapes of these antibody binding curves showed that the antigenic determinants recognized by the two monoclonal antibodies were present at high density on the P3 carcinoma but at low density or absent from the PL3. The immunoglobulin isotype of both 169D4 and 169F3 monoclonal antibodies was identified as IgM. The two monoclonal antibodies were tested for binding to 12 carcinoma cell lines, 9 melanoma, 2 sarcoma, 4 lymphoblast, and 1 human embryonic. Among the cell lines tested, only the lung carcinoma P3 and the colon carcinoma HT29 expressed detectable levels of 169D4 surface antigen. 169F3 monoclonal antibody recognized an epitope present on every human tumor cell line and on human embryo cells, but not on the lymphoblastoid cell lines. (6 Refs)

65. METHODS FOR PRODUCTION OF MONOCLONAL ANTIBODIES WITH SPECIFICITY FOR HUMAN LUNG CANCER CELLS.

Minna JD, Cuttitta F, Rosen S, Bunn PA, Carney DN, Gazdar AF, Krasnow S

NCI-Veterans Admin. Branch, Div. Cancer Treatment, NCI, Washington, DC

In Vitro; 17(12):1058-1070 1981

We have developed a screening strategy and technology to produce monoclonal antibodies with specificity for human lung cancer cells. Mice and rats were immunized with well-characterized tissue culture lines of human small cell lung cancer (SCLC), mouse myeloma x spleen hybrids formed by the technique of Kohler and Milstein, and the resulting culture fluids were screened for antibody binding phenotype using a radioimmunoassay. To facilitate testing large numbers of culture fluids, a 96-well, microtiter based, re-usable, replicating device was designed. Using this, many hybridoma culture fluids were replica plated for antibody binding tests on a series of human target cell plates. Hybrids producing antibodies that reacted with the immunizing SCLC line and another independent SCLC line, but not with autologous B-lymphoblastoid cells derived from one of the patients, were identified, selected, and then repeatedly recloned using the same screening strategy. With this technology, hybridomas representing less than 0.5% of all hybrids generated could be isolated and stable antibody producing cultures derived. Such antibodies reacted with a panel of well-characterized SCLC lines and SCLC samples taken directly from patients but not with a variety of normal tissues. Using these antibodies we can demonstrate: tumor cell contamination of bone marrow specimens, marked heterogeneity of antigen expression on cells within individual SCLC lines and individual patients, and inhibition of clonal growth of SCLC lines in soft agarose assays. All of these findings have potential clinical and cell biologic application. (Author abstract) (50 Refs)

66. MONOCLONAL ANTIBODY AGAINST A1 LEWIS D ANTIGEN PRODUCED BY THE HYBRIDOMA IMMUNIZ ED WITH A PULMONARY CARCINOMA.

Iwaki Y, Kasai M, Terasaki PI, Bernoco D, Park MS, Cicciarelli J, Heintz R, Saxton RE, Burk MW, Morton DL

Dept. Surgery, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024

Cancer Res; 42(2):409-411 1982

A monoclonal antibody (CALed) against a human pulmonary squamous cell carcinoma line was cytotoxic to the line but did not react to an autologous B-lymphoblastoid line. Although the antibody was thought to be cancer specific, principally on the basis of this evidence, the antibody actually had the A1 Lewis d (Led) specificity. It reacted with approximately 2% of the random donor T-lymphocytes and with all six lymphocytes from donors who were A1 Led type without reacting to lymphocytes of any other type. The monoclonal antibody reactivity was also absorbed out by A1 Led red blood cells but not by red cells of other types. We conclude that the A1 Led antigen had been synthesized by the pulmonary carcinoma lines but not by the autologous lymphoblastoid line, resulting in disparity for this antigen. Since the combination A1 Led only occurs in 2% of the population, it is difficult to distinguish this type of antibody from tumor-specific antibodies. (Author abstract) (14 Refs)

67. ANTIGENS OF HUMAN PANCREATIC ADENOCARCINOMA CELLS DEFINED BY MURINE MONOCLONAL ANTIBODIES.

Metzgar RS, Gaillard MT, Levine SJ, Tuck FL, Bossen EH, Borowitz MJ
Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27710
Cancer Res; 42(2):601-608 1982

We have elicited and characterized the serological specificity of five murine monoclonal antibodies (DU-PAN-1, 2, 3, 4, and 5) to a human pancreatic tumor cell line, HPAF. The antibodies are not detecting HLA-associated antigens since all of the monoclonals failed to react with human lymphoid and myeloid cell lines and uncultured cells. All of the monoclonals except DU-PAN-5 reacted with four of five pancreatic tumor cell lines and two of two uncultured pancreatic tumors. An immunoperoxidase technique was used to determine the presence of the antigens detected by the monoclonal antibodies in frozen sections of tumor and adult and fetal normal tissues. DU-PAN-1 antigen was detected on pancreatic tumors, and a transitional cell carcinoma of the bladder, but was detected on no other adult or fetal normal tissues including pancreas. One of the antigens (DU-PAN-2) defined by the monoclonals was present on pancreatic ductal epithelial cells and showed a restricted distribution on tumor cells from some other carcinoma patients and on cells from certain fetal tissues. DU-PAN-3 antigen was present on adult and fetal pancreatic cells and certain tumor cells but could not be detected on cells of other fetal or adult normal tissues. DU-PAN-4 and DU-PAN-5 antigens have a more widespread distribution on normal or tumor cell types. (Author abstract) (9 Refs)

68. DETECTION OF HUMAN OSTEOSARCOMA-ASSOCIATED ANTIGEN(S) BY MONOCLONAL ANTIBODIES.

Hosoi S, NakamuraT, Higashi S, Yamamuro T, Toyama S, Shimomiya K, Mikawa H
Dept. Pediatrics, Univ. Kyoto, Sakyo-ku, Kyoto 606, Japan
Cancer Res; 42(2):654-659 1982

Hybrid cell lines have been derived from a fusion between mouse myeloma cells, NS1, and spleen cells from mice immunized with freshly resected osteosarcoma cells from an untreated patient. Of the 276 hybrids obtained, five secreted antibodies which bound to osteosarcoma tissues but not to autologous skin fibroblasts. The antibodies from three of these five hybrids, OST6, OST7, and OST15, reacted with all of five osteosarcoma tissues and with one chondrosarcoma tissue but not with other malignant or benign tumors. Tests of various normal tissues were negative, except for weak binding to a subpopulation of chondrocytes in articular cartilage. The reciprocal binding inhibition test showed that OST6, OST7, and OST15 antibodies were directed against different antigenic determinants. (Author abstract) (24 Refs)

69. ADCC OF CULTURED HUMAN MELANOMA CELLS: ANALYSIS WITH MONOCLONAL ANTIBODIES TO HUMAN MELANOMA-ASSOCIATED ANTIGENS.

Imai K, Ng AK, Glassy MC, Ferrone S
Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, La Jolla, CA
Scand J Immunol; 14(4):369-377 1981

Four monoclonal antibodies to human melanoma-associated antigens (MAA) were found to be able to mediate specific cell-dependent lysis (ADCC) of cultured human melanoma cells. The extent of specific lysis of melanoma cells was influenced by the effector to target cell ratio, the amount of antibody added to the reaction mixture, and the incubation time. Cultured melanoma cells treated for 16 hr with puromycin or cycloheximide (final concentration, 1.0 ug/ml) displayed increased susceptibility to ADCC even though the cell surface expression of MAA was not changed. On the other hand, treatment of melanoma cells with tunicamycin (final concentration, 1.0 ug/ml) reduced the expression of MAA but did not affect susceptibility to ADCC. These findings suggest that other properties of the target cell membrane besides antigen density play a role in the outcome of ADCC reaction. (Author abstract) (16 Refs)

70. CELLULAR DISTRIBUTION OF MONOCLONAL ANTIBODY IN HUMAN TUMOURS AFTER I.V. ADMINISTRATION.

Moshakis V, McIlhinney AJ, Neville AM
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Br J Cancer; 44(5):663-669 1981

Immune-suppressed mice carrying xenografts of several different types of human germ-cell tumors were injected with a radiolabelled monoclonal antibody (LICR LON/HT13) raised against membrane components of a human germ-cell tumor (HX39). Subsequent assessment of radioactivity in excised organs and tumors showed a selective accretion of antibody in the tumor. Quantitative autoradiography supported the results of radiolocalization observed in vivo in different tumors, and also showed that the antibody localized to viable tumor cells and in close association with their cell membrane. The vascular architecture of tumors was found to be an important factor governing antibody distribution. No localization occurred with radiolabelled normal mouse IgG. (Author abstract) (13 Refs)

71. INDUCTION OF IMMUNE CYTOLYSIS: TUMOR-CELL KILLING BY COMPLEMENT IS INITIATED BY COVALENT COMPLEX OF MONOCLONAL ANTIBODY AND STABLE C3/C5 CONVERTASE.

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Proc Natl Acad Sci USA; 78(12):7707-7711 1981

The unique specificity of monoclonal antibodies (Ab) was combined with the cell-killing function of the cytolytic alternative pathway of complement. The functionally C3b-like glycoprotein of cobra venom was linked to a murine monoclonal Ab directed to a human melanoma-associated antigen by a disulfide bond, by using a heterobifunctional crosslinking reagent. The covalent monoclonal Ab-cobra venom factor (CVF) complex exhibited specific cytolytic activity in the presence of normal or C4-deficient serum. It induced killing of melanoma cells but not of LG-2 lymphoblastoid cells or P815 mastocytoma cells. The cytolytic action of the monoclonal Ab-CVF complex was selective in that it was limited to the melanoma cells when these were mixed with one of the two other cell lines. In absence of serum, the complex was noncytotoxic. Monoclonal Ab or CVF alone had no cytolytic activity with or without serum. It is concluded that CVF covalently linked to melanoma cell-bound Ab forms the stable C3/C5 convertase with factors B and D of the alternative pathway, which in turn causes formation of the membrane attack complex and thereby cell death. (Author abstract) (32 Refs)

72. IMMUNOLOGICAL DELINEATION IN NORMAL AND MALIGNANT CELLS OF A MEMBRANE PROTEIN INVOLVED IN GLUCOSE TRANSPORT. I. PREPARATION AND PROPERTIES OF THE ANTIBODY.

Gingrich RD, Wouters M, Bramwell ME, Harris H
Sir William Dunn Sch. Pathology, South Parks Road, Oxford OX1 3RE, England
J Cell Sci; 52:99-120 1981

Partially purified preparations of the 200,000 Mr membrane glycoprotein described by Bramwell and Harris were used as antigens to generate monoclonal antibodies. Whether the protein was prepared from human or mouse tumors, the mice immunized with it yielded monoclonal antibodies of broadly similar specificities. All the antibodies obtained were of the immunoglobulin M class, despite a prolonged immunization schedule, and recognized an antigen that was present on the surface of mouse, rat and human cells. One such antibody, M/27, was studied in detail. With the exception of two rat kidney cell lines, the antigen detected by M/27 was found on the surface of all cells grown in culture, whether malignant or not. However, in the mouse, the species in which the antibody was generated, M/27 discriminated sharply between malignant tumors and normal tissues excised directly from the animal. In normal adult or embryonic mouse tissues, whether they were composed of multiplying cells or not, the antigen detected by M/27 was present on the cell surface only at the lower limit of detection, if at all. Malignant mouse tumors grown in the animal produced large amounts of the antigen. Explanation of embryonic mouse fibroblasts induced the expression of the antigen, which was not detected on these same cells in their normal habitat in the growing embryo. Conversely, non-malignant cells that express the antigen in vitro cease to do so when they are re-introduced into the animal. The antigenic determinant appeared to be polypeptide in nature rather than polysaccharide. (Author abstract) (40 Refs)

73. PRODUCTION AND CHARACTERIZATION OF MONOCLONAL ANTIBODIES AGAINST THE EPSTEIN-BARR VIRUS MEMBRANE ANTIGEN.

Strnad BC, Schuster T, Klein R, Hopkins RF, Witmer T, Neubauer RH, Rabin H
Frederick Cancer Res. Center, Frederick, MD, 21701
J Virol; 41(1):258-264 1982

Five murine hybridoma lines that produce monoclonal antibodies against Epstein-Barr virus membrane antigen (MA) were established. Immunoprecipitation experiments demonstrated that three of the antibodies precipitated both the 236,000 (236K) MA and the 212K MA. The other two antibodies precipitated the 86K MA. Antibodies against the 236K-212K MA and the 86K MA mediated complement-dependent cytolysis of Epstein-Barr-virus-infected cells. The antibodies against the 86K MA neutralized both the B95-8 and P3HR-1 viruses. (Author abstract) (18 Refs)

74. TISSUE DISTRIBUTION, MOLECULAR PROFILE, AND SHEDDING OF A CYTOPLASMIC ANTIGEN IDENTIFIED BY THE MONOCLONAL ANTIBODY 465.12S TO HUMAN MELANOMA CELLS.

Natali PG, Wilson BS, Imai K, Ligotti A, Ferrone S
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Cancer Res; 42(2):583-589 1982

The mouse immunoglobulin G2 monoclonal antibody (MoAb) 465.12S reacts with a cytoplasmic antigen present in human melanoma cells but not detectable in melanocytes. Indirect immunofluorescent staining of a large number of surgically removed normal adult and fetal tissues with the MoAb 465.12S detected the cytoplasmic antigen in epithelial cells from several organs. The intensity of staining was greater in adult tissues than in the corresponding fetal tissues. Furthermore, the MoAb 465.12S stained nearly all of the surgically removed tumors tested but did not stain many of the normal tissues from which they originated. In almost all cases, the intensity and frequency of staining was greater for tumor cells than for corresponding normal tissues. From cultured carcinoma and melanoma cells, the MoAb 465.12S immunoprecipitated four glycopolypeptides with mol wt of 94,000, 75,000, 70,000, and 25,000. Incorporation of 3H-labeled sugars into the various components of the cytoplasmic antigen revealed that the MW 75,000 component was unusual in that it contained only glucosamine and mannose. The antigenic determinant defined by the MoAb 465.12S appears to be protein rather than carbohydrate in nature since it is heat sensitive and is expressed on the antigens synthesized by cells in presence of tunicamycin. Analysis of the spent culture medium of carcinoma and melanoma cell lines revealed that the cytoplasmic antigen is readily shed by these cells and consists of a major MW 94,000 and a minor MW 72,000 component. Treatment of cultured melanoma cells with the antibiotic tunicamycin showed that glycosylation of the cytoplasmic antigen is required for its shedding and/or stability in the spent culture medium. (Author abstract) (30 Refs)

75. A MONOCLONAL ANTIBODY THAT DEFINES AN IDIOTOPE WITH TWO SUBSITES IN GALACTAN-BINDING MYELOMA PROTEINS.

Pawlita M, Muschinski E, Feldmann RJ, Potter M
Lab. Cell Biology, NCI, NIH, Bethesda, MD, 20205
J Exp Med; 154(6):1946-1956 1981

The monoclonal antibody HyX24-14 that binds different galactan-binding myeloma proteins (GalBMP) of BALB/c mice with different affinities is described. Amino acid sequence data and hypothetical topographical models were used to partially outline the binding site for the monoclonal antibody on GalBMP. HyX24-14 was derived from an A/J mouse that had been immunized with the X24 GalBMP. Binding affinities were determined for four GalBMP whose variable regions had been completely sequenced; affinity was highest for X24, medium for X44, low for T601, and nondetectable for J539 GalBMP. A structural explanation was proposed for the observed binding activities of HyX24-14. Jk region sequence differences should not directly cause the observed affinity differences because positions 96, 100, and 106 are inaccessible to the surface. Because X24 and T601 have identical L chains up to position 100L, sequence differences in the variable region of the heavy chain and those in the D region are probably responsible for affinity differences. HyX24-14 may interact with a relatively large surface of the GalBMP that includes both parts of CDR-2 and CDR-3 (the D region) of the heavy chain. From molecular models and amino acid sequence data, it is proposed that the idiotope defined by HyX24-14 has two subsites, each of which appears able to bind independently to the antibody. (19 Refs)

76. SPECIFICITY OF SYNGENEIC MONOCLONAL ANTIBODIES AGAINST CELL SURFACE ANTIGENS ON CHEMICALLY INDUCED MOUSE FIBROSARCOMAS.

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Transplant Proc; 13(4):1762-1764 1981

Development and characterization of 16 monoclonal antibodies (McAb) against tumor-specific transplantation antigens (TSTA) are reported. McAb were developed by immunizing C57BL/6 and BALB/c mice with their own syngeneic, chemically induced fibrosarcomas bearing unique TSTA; the formation of hybridomas followed. Radioimmunoassays were carried out with a large panel of normal cells, tumor cells, and ecotropic and xenotropic murine leukemia viruses (MuLV). Competitive binding assays used tumor cells and MuLV against well-characterized anti-MuLV gp70 and p15(E) McAb. No highly restrictive tumor specificity was found for any of 16 McAb tested. All McAb showed either MuLV-dependent or MuLV-independent cross-reactivity with several mouse tumor strains. Results obtained with five McAb are tabulated. Reactions to anti-MuLV indicated that M3, PC11, and CS-1 tumor strains express gp70 and p15(E) antigens of ecotropic and/or xenotropic viruses on the cell surface. McAB L1 and 4B1 were specific for tumors bearing MuLV antigens. The 4B1 McAb was specific for a molecule similar or identical to the gp70a epitope of ecotropic MuLV. Three McAb showed tumor reactions independent of MuLV antigens. Failure to produce a tumor-specific McAb may be due to differences in T and B cell function or to sampling luck. (9 Refs)

77. HYBRIDOMA MONOCLONAL ANTIBODIES IN THE ANALYSIS OF HUMAN CELL SURFACE ANTIGENS.

Levy R, Bergman Y, Finn O
Dept. Medicine, Div. Oncology, Stanford Univ. Medical Center, Stanford, CA, 94305
In Vitro; 17(12):1051-1057 1981

In the present paper, we will summarize studies we have performed on two distinct human lymphocyte cell surface antigens defined by monoclonal antibodies: Leu-1 and HLA-DR. (Author abstract) (27 Refs)

78. MONOCLONAL ANTIBODIES AGAINST RECEPTOR FOR EPIDERMAL GROWTH FACTOR INDUCE EARLY AND DELAYED EFFECTS OF EPIDERMAL GROWTH FACTOR.

Schreiber AB, Lax I, Yarden Y, Eshhar Z, Schlessinger J
Dept. Chemical Immunology, Weizmann Inst. Science, 76100 Rehovot, Israel
Proc Natl Acad Sci USA; 78(12):7535-7539 1981

Mice were immunized with human epidermoid carcinoma cells (A-431 cell line) that possess an unusually high number of membrane receptors for epidermal growth factor (EGF). Spleen cells from these mice were fused with NSI cells, a non-secreting murine myeloma. The immunoglobulins secreted by the obtained hybridomas were screened for specific binding to A-431 cells and selected according to their ability to inhibit the binding of radiolabeled EGF to the membrane of A-431 cells. Several antibodies secreted by cloned hybrid lines were found to inhibit the binding of radiolabeled EGF to membrane receptors of living A-431 cells, human foreskin fibroblasts, and mouse 3T3 fibroblasts and also to membrane preparations from A-431 cells. These monoclonal antibodies induced the early and delayed biological effects mediated by EGF. Like EGF, the antibodies induced morphological changes in A-431 cells and enhanced the phosphorylation of endogenous membrane proteins in membranes from these cells. They also stimulated DNA synthesis in human foreskin fibroblasts. These observations support the notion that the biological information of the EGF-receptor complex resides in the membrane receptor. Furthermore, the antibodies offer a powerful tool to study the structure, processing, and mode of action of EGF receptors. (Author abstract) (34 Refs)

79. PRODUCTION OF MONOCLONAL ANTIBODIES AGAINST MM ANTIGEN: THE SEROLOGIC IDENTIFICATION OF MM ANTIGEN WITH LY-6.2 ALLOANTIGEN.

Seto M, Takahashi T, Tanimoto M, Nishizuka Y
Lab. Experimental Pathology, Aichi Cancer Center Res. Inst., Chikusa-ku, Nagoya 464, Japan
J Immunol; 128(1):201-205 1982

Monoclonal antibodies against MM46, an ascitic mouse mammary tumor of C3H/He, were produced by fusing mouse myeloma cell line NS-1 with spleen cells from a (BALB/c x C3H/HeN)F1 mice hyperimmunized with MM46, an MM antigen-positive tumor. Eight antibodies showed cytotoxicity against MM46, but not against MM48, an MM antigen-negative ascitic mammary tumor, and one hybridoma produced an agglutinating antibody. One of the cytotoxic monoclonal antibodies, 3-3-C, was selected, and the strain distribution and the tissue distribution of MM antigen were studied. The results demonstrated that MM antigen had a strain distribution identical to Ly-6.2 antigen, and a similar tissue distribution. Therefore, the characterization of MM antigen and Ly-6.2 antigen was investigated. Ly-6.2 antibody was shown to be cytotoxic for MM46, but not for MM48, in accordance with 3-3-C. Genetic segregation analysis of MM and Ly-6.2 antigens in 33 backcross mice demonstrated complete concordance between these two antigens. In addition, MM antigen phenotype of an Ly-6.2 congenic strain, C3H.B6-Ly-6b, was studied, and it was found to be positive in contrast to C3H/HeN. Furthermore, cross-absorption studies revealed that both MM46 cells and C3H.B6-Ly-6b lymph node cells could absorb cytotoxic activities of 3-3-C and monoclonal anti-Ly-6.2 antibody. The results so far obtained suggested strongly that these two loci controlling expression of MM and Ly-6.2 antigens were identical or very closely linked. (Author abstract) (26 Refs)

80. SPECIFIC ANTIGENS ON METHYLCHOLANTHRENE-INDUCED TUMORS OF MICE.

Lennox ES, Lowe AD, Cohn J, Evan G
MRC Lab. Molecular Biology, Hills Road, Cambridge, CB2, 2QH, England
Transplant Proc; 13(4):1759-1761 1981

Development of monoclonal antibodies to B10/MC6A (6A) mouse sarcoma is reported. A B10 mouse was immunized with tumor cells. Spleen cells from the immunized mouse were fused with myeloma cells to form hybrid cells. Hybrids producing antibodies to tumor-specific transplantation antigens (TSTA) were selected by assays using cells from lines 6A and B10/MC6B (6B: a tumor line not cross-reacting with 6A). One monoclonal antibody designated 4B1 was tested for specificity for tumor line 6A. Although 4B1 showed 10-20% cross-reaction in transplantation assays, 6B did not cross-react with 6A. Assays using B6 and BALB/c tumors detected several 4B1-positive tumor lines, two of which showed cross-protection. An assay using immunized B10 mice showed that immunization with cells from either of two 4B1-positive tumor lines protected the mice against challenge by 6A cells; cells from a 4B1-negative line did not. Evidence suggests a correlation between the 4B1 antigen and the TSTA of the 6A tumor line. The molecule carrying 4B1 specificity is a protein with approx mol wt of 70,000; the protein carries the a-epitope of the gp70 retrovirus envelope protein, which is recognized by the previously reported antibody anti-gp70 16B7. Both the 16B7 and 4B1 antigens appear on the same cells, and each blocks binding of the other. Findings suggest that specificity of TSTA is carried on gp70-like molecules. (7 Refs)

81. ANTIGENS ON NATURALLY OCCURRING ANIMAL AND HUMAN TUMORS DETECTED BY MONOCLONAL ANTIBODIES.

Embleton MJ, Gunn B, Byers VS, Baldwin RW, Bonavida B, Martin WJ, Ferrone S
Cancer Res. Campaign Lab., Univ. Nottingham, Nottingham, NG7.2RD, England
Transplant Proc; 13(4):1966-1969 1981

Reactivities of monoclonal antibodies prepared against a spontaneously arising rat mammary carcinoma and human osteogenic sarcoma cells were studied. An antibody-secreting hybridoma was prepared by fusion of the mouse myeloma P3-NS1-Ag4 (P3NS1) with spleen cells from rats immunized against a syngeneic mammary carcinoma, Sp4. The monoclonal antibody produced reacted only with mammary carcinoma Sp4 and did not bind to other rat tumors or normal rat cells. Two cell lines (791T/36 and 791T/48) from hybridomas obtained by the fusion of spleen cells from BALB/c mice immunized with the 791T osteogenic sarcoma cell line with P3NS1 cells, produced antibody that reacted preferentially with 791T cells. Antibody 791T/36 reacted strongly with 791T cells and with another osteogenic sarcoma, 788T, and more weakly with two others, 805T and 845T; the antibody did not react with six other osteogenic sarcomas. Tests against 11 lines of cultured fibroblasts, including 3 lines derived from the donor of 791T and 2 from donors of cross-reactive sarcomas, were negative. Monoclonal antibody from 791T/48 gave different cross-reactions. Two different monoclonal antibodies to a human osteogenic sarcoma cell line reacted with the immunizing cell line but not with cultured fibroblasts from the tumor host. Neither showed specificities for blood group or D-locus antigens. Despite apparent tumor association, the antigens detected by the monoclonal antibodies were not shared by all osteogenic sarcomas and were not restricted to this tumor type. (10 Refs)

82. ALIEN HISTOCOMPATIBILITY ANTIGENS AND ALLOIMMUNIZATION: CONCEPTUAL AND PRACTICAL CONSIDERATIONS.

Bach FH, Bortin MM
Immunobiology Res. Center, Univ. Minnesota, Box 724 Mayo Memorial Building, Minneapolis, MN, 55455
Transplant Proc; 13(4):1975-1978 1981

Problems associated with the definition of alien histocompatibility antigens (AHA) and antigens cross-reactive with alloantigens (ACRA) are described. The first serologic evidence of AHA cannot be used as positive identification of an antigen that is identical with an alloantigen in its primary sequence. By isolating AHA on a syngeneic tumor cell line with the aid of alloantiserum and subsequent peptide mapping, it has been possible to demonstrate that AHA is at least in part identical with the alloantigen. Monoclonal antibodies have been used to study the cross-reactivity of AHA. Mechanisms that could be involved in the expression of genes in abnormal cells which are expressed in normal cells are discussed. Differentiation of AHA from other syngeneic or autologous abnormal cell antigens that have primary structural homology with alloantigens (ACRA) are described. Cloned cytotoxic T lymphocytes have been used for the identification of ACRA. Tumor contamination may be a problem in the study of ACRA expression. Adoptive transfer experiments resulting from the discovery of the possible existence of AHA and ACRA are described. HLA matching for bone marrow transplantation and adoptive immunotherapy is discussed. The existence of AHA is considered. (6 Refs)

83. MONOCLONAL ANTIBODIES AGAINST MYCOPLASMA HYORHINIS. A SECONDARY EFFECT OF IMMUNIZATION WITH CULTURED CELLS.

Vennegoor C, Polak-Vogelzang AA, Hekman A
Dept. Immunology, Netherlands Cancer Inst., 1066 CX Amsterdam, The Netherlands
Exp Cell Res; 137(1):89-94 1982

Monoclonal antibodies were prepared against two different human tumor cell lines, the melanoma cell line SK-Mel-25 and the acute lymphoblastic leukemia T cell line CCRF-CEM. Presence of antibodies against human tumor cells in the supernatants of hybridoma cultures was tested by binding of 125I-F(ab')2 anti-mouse IgG. On two occasions a hybridoma culture, initially selected for subsequent cloning as it seemingly produced antibodies against tumor cells, was later found to produce monoclonal antibodies specific for Mycoplasma hyorhinis. In immunofluorescent staining patchy structures were visible which seemed to be attached to the cell surface. By combined staining with FITC-conjugated anti-mouse immunoglobulin for monoclonal antibody, Evans blue for cytoplasm and Hoechst compound number 33258 for DNA, the reaction against mycoplasma could be recognized. These results demonstrate that if cultured cells are used for preparation of monoclonal antibodies, there is a good chance that the selected hybridomas may produce antibodies against 'culture artifacts' such as mycoplasmas, in addition to the target antigens. Thus mycoplasma contamination of cell cultures poses a serious problem in the hybridoma research and the testing system for antibody specificity should be carefully monitored. (Author abstract) (36 Refs)

ANIMAL MODELS OF BIOLOGICAL THERAPY

84. TUMOR SPONGE IMPLANTATION: AN IN VIVO METHOD FOR STUDYING SYNGENEIC, PRIMARY ANTITUMOR LYMPHOCYTE RESPONSES.

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Dept. Lab. Medicine and Pathology, Univ. Minnesota, Box 367, Mayo Memorial Building, Minneapolis, MN, 55455
Cancer Res; 42(2):397-404 1982

Sponge matrices surgically implanted in the sc, space of the bank or normal BALB/c mice were injected with a 'regressor' dose of Moloney virus-induced BALB/c tumor cells. The kinetics of the generation of cytotoxic cells within the sponge was studied over a 22-day period in a short-term 51Cr release assay. Cytotoxic activity peaked on Day 16 and then declined to negligible levels by Day 22. When the cellular composition of implanted tumor sponges was examined on Day 16, it was found to be 30 to 40% myeloperoxidase-positive cells, 15 to 25% surface Ig-positive cells, and 40 to 50% theta-positive cells. Treatment with anti-Thy 1.2 plus complement eliminated the cytotoxic response on Day 16. The ratio of T-cells to tumor cells within the sponge was determined by immunofluorescence. Kinetic studies showed that the number of theta-positive cells increased well before cytolytic activity was detected, possibly reflecting increasing numbers of amplifier T-cells or cytotoxic cell precursors. A later decline in theta-positive cells correlated directly with decreased cytotoxicity. Furthermore, onset of cytotoxic activity also correlated with a decline in the percentage of Moloney murine sarcoma virus tumor cells within the sponge. Sponge cells isolated on Day 16 (peak cytotoxicity), mixed with lethal dosages of Moloney murine sarcoma virus tumor cells, successfully neutralized the lethal challenge demonstrating the in vivo antitumor efficacy of these effector cells. Sponges were also implanted in mice which had been immunized with a single injection of Moloney murine sarcoma virus cells. Inoculation of the sponge with tumor cells resulted in a second set response in which cytotoxic cells appeared much earlier than in unsensitized animals. Cells from spleen, lymph node, or peritoneal cavity of normal or presensitized animals with tumor sponge implants were not cytotoxic, suggesting a highly localized response. (33 Refs)

85. ANAPLASTIC CARCINOMA IN THE BUCCAL POUCHES OF HAMSTERS AS A MODEL OF ORAL CANCER.

Meng CL, Albright J, Shklar G
Dept. Oral Medicine and Oral Pathology, Harvard Sch. Dental Medicine, Boston, MA
J Dermatol Surg Oncol; 7(12):1011-1017 1981

An experimental model of oral cancer was developed. Adult Syrian hamsters were subjected to applications of a 0.5% soln of 7,12-dimethylbenzanthracene (DMBA) to the mucosa of the buccal pouch. The DMBA-induced epidermoid carcinomas were transplanted to the abdominal cavities of newborn hamsters. Abdominal tumors were detected 8 wk after transplantation. The first-generation abdominal tumors were subjected to serial replantation in the abdominal cavities and buccal pouches of immunosuppressed or non-immunosuppressed hamsters. The original DMBA-induced tumors of the oral mucosa had histology of well-differentiated carcinoma. After serial transplantation, tumors became anaplastic. The anaplastic epidermoid carcinomas could be replanted to the buccal pouches of both immunosuppressed and non-immunosuppressed hamsters. No metastatic spread from the tumors in buccal pouches was found. (13 Refs)

86. THE EFFECT OF ADJUVANT IMMUNOTHERAPY ON TUMOR RECURRENCE AFTER SEGMENTAL RESECTION OF CARCINOGEN-INDUCED WISTAR/FURTH PRIMARY BOWEL ADENOCARCINOMAS.

Steele G, Harte PJ, Rayner AA, Corson JM, Madara J, Munroe AE, King VP, Wilson RE
Brigham and Women's Hosp., 75 Francis St., Boston, MA, 02115
J Immunol; 128(1):7-10 1982

Primary bowel tumors were induced in Wistar/Furth (W/Fu) rats by 16 weekly sc injections of 1,2-dimethylhydrazine (DMH). After 'curative' resection of primary adenocarcinomas of the colon, 75% of control rats who received no further treatment developed local or regional recurrence within 22 wk. In four separate experiments, rats immunized after primary tumor resection by three weekly sc inoculations of 1 x 10(6) irradiated (10,000 rad) DMH-W15 sarcoma cells (no tumor-associated antigens cross-reacting with bowel adenocarcinomas) developed recurrent tumor at a rate similar to the controls. By contrast, after primary bowel tumor resection, rats immunized with DMH-W163 colon adenocarcinoma (possessing tumor-associated antigens cross-reactive with other W/Fu bowel adenocarcinomas) showed a consistently reduced rate of local or regional recurrence compared to either of the controls (chi2 = 4.62, p less than 0.05) or the rats immunized with sarcomas (chi2 = 5.42, p less than 0.05). By 22 wk after primary tumor resection, only 35% of the DMH-W163-immunized animals in each of the four experiments showed recurrence. No deaths from recurrences were noted in any of the experimental groups after this time, and selected animals sacrificed in the immunized groups up to 30 wk after primary tumor resection were documented to be disease-free. Protection against tumor recurrence was, therefore, a reflection of increased disease-free survival. No change in the effectiveness of immunoprotection in this model could be demonstrated after resection of less invasive primary tumors. These data reflect the utility of a new model in which modification of the natural history of individual primary bowel adenocarcinomas can be examined. The similarities and differences between this system and humans with colon cancer are discussed. (Author abstract) (13 Refs)

CLINICAL IMMUNOLOGY

87. CELL-MEDIATED IMMUNITY IN BREAST CANCER PATIENTS IN RELATION TO CLINICAL STAGES.

Pasqualini RS, Giraudo Concsa LC, Lynch M, Sardi J, Pujato D
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Cell Mol Biol; 27(5):551-556 1981

Cell-mediated immunity of patients with breast cancer at clinical stage I, II, III or IV, prior to any therapy, was evaluated in relation to their clinical stage. In vitro peripheral blood studies included: absolute number of lymphocytes/ul; absolute number of T-lymphocytes/ul (E-rosette-forming cells); lymphocytes' response to phytohemagglutinin. In vivo assays consisted of delayed hypersensitivity skin tests to ubiquitous antigens and 2,4-dinitrochlorobenzene sensitization. The results obtained can be summarized as follows: absolute numbers of total lymphocytes/ul were lower in breast cancer patients than in the normal group. However, the values corresponding to Stage IV were the only ones significantly different when compared with normal and with any other clinical stage. Absolute numbers of T-lymphocytes/ul were lower in breast cancer patients than in the normal group, and statistically significant differences were found when Stages II, III or IV were each compared with the normal group. Furthermore, a significant decrease in the number of T-lymphocytes was observed in Stage IV, as compared with any other clinical stage. Transformation indices obtained from lymphocyte cultures of patients were lower than those observed in normals. However, the values corresponding to Stage I were the only ones significantly different. Moreover, the transformation index of Stage I was also significantly lower than that of Stage IV. The percentages of positive skin tests to purified protein derivative were significantly lower in Stage II, III or IV than in either Stage I or the normal group. The percentage of positive skin tests to Candida albicans antigen was significantly decreased in Stage IV. Finally, the percentages of positivity to 2,4-dinitrochlorobenzene sensitization were lower in all clinical stages of breast cancer than in the normal group. In Stage II, immune competence was not affected by metastatic involvement of regional lymph nodes. The observed differences cannot be attributed to age. (Author abstract) (27 Refs)

88. MAXIMIZING DIFFERENCES IN THE CONCANAVALIN A-INDUCED BLASTOGENIC RESPONSES OF LYMPHOCYTES FROM BREAST CANCER PATIENTS AND CONTROLS BY THE USE OF ALPHA-METHYL-D-MANNOSIDE.

Distasio JA, Cheresh DA, Schilder RJ, Vogel CL, Silverman MA, Lopez DM
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JNCI; 68(1):69-74 1982

In an attempt to magnify differences in the immune responses of potentially immunosuppressed cancer patients and normal controls, an assessment was made on the effects of the competitive inhibitor alpha-methyl-D-mannoside on the concanavalin A (Con A)-induced blastogenic responses of lymphocytes from each of these populations. Lymphocytes from breast cancer patients with metastatic disease were significantly deficient in their capability to undergo blast transformation regardless of whether the monosaccharide inhibitor was added to the assay cultures. In contrast, lymphocytes from breast cancer patients who did not display metastatic disease were capable of normal blastogenic responses to Con A. The addition of alpha-methyl-D-mannoside to lymphocyte cultures caused a significantly greater inhibition of the blastogenic responses of these patients' cells as compared to cells of normal controls. Thus the monosaccharide seems to serve as a useful reagent for optimizing differences between lymphocyte blastogenic responses of normal donors and those of immunodepressed donors. The results suggest that lymphocytes from breast cancer patients without clinically evident metastases possess some modification of their cell membrane. One possibility discussed was that the number or distribution of receptors for Con A on the membrane of lymphocytes of these patients is deficient. (Author abstract) (27 Refs)

89. PROGNOSTIC INTEREST OF LOCO-REGIONAL IMMUNITY IN PATIENTS BEARING MAMMARY CARCINOMA (MEETING ABSTRACT).

Bourguignat A, Touze ME, Beuzelin M, Leducq J, Pallud C, Desplaces A, Saracino RT
Centre Rene Huguenin, Saint-Cloud, France
Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

Lymph-node invasion is a primordial prognostic factor for patients suffering from breast cancer. If a host-tumor immune response exists, then the most probable sites for this reaction in this type of cancer are the axillary lymph-nodes. The present study was therefore undertaken to investigate any eventual modifications in the lymphoid populations in these lymph-nodes. We have studied: 1) the fraction of T-lymphocytes which form autologous rosettes; and 2) the sub-populations of T-cells as defined by the commercial monoclonal antibodies: OKT3 (peripheral blood cells), OKT4 (Helper), OKT6 (thymocytes), OKT8 (suppressor and cytotoxic). The ratio of the level of autologous rosette-forming -cells in the lymph-node to the level of autologous rosette-forming-cells in the blood is less than 1 in the absence of lymph-node invasion and always greater than 1 in the presence of invasion. There is no quantitative difference in the OKT3+, OKT4+ and OKT8+ populations in non-invaded or invaded nodes. On the other hand, it seems that the OKT8+ population is greater in the draining lymph-nodes surrounding the tumor than in control lymph-nodes. (no Refs)

90. IMMUNOLOGICAL MARKER ANALYSIS IN 389 PATIENTS WITH LYMPHOID LEUKAEMIA (MEETING ABSTRACT).

van der Reijden HJ, Van der Griend RJ, Van de Rijn JM, Van Wering ER, Behrendt H, Bos MJ, Veer MB, Melief CJ, Borne AE
Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, Netherlands
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

The cells of 39 adult patients with acute lymphoid leukemia (ALL) including 3 with leukemized non-Hodgkins lymphoma (NHL), 120 children with ALL, including 6 with leukemized NHL and 230 patients with chronic lymphoid leukemia (CLL) were investigated with a large number of conventional surface marker tests and monoclonal reagents, including the Ortho series. The leukemia of about 25% of the patients with ALL was classified as T-ALL (both in childhood and in adult ALL), while B-ALL comprized only 4-8% in both groups. cALL positive nT-nB ALL was the most frequent form of childhood ALL (66%), with only 30% cALL positive leukemias in the adult group. The real null variant of the nT-nB ALL was the most frequent ALL in adult ALL (48%; 11% in childhood). Virtually no Ia negative leukemias were found in the Null cell group. Leukemized lymphoblastic NHL was characterized in all cases as a T-cell proliferation (E+ or E-). Chronic lympho-proliferative disease was classified as B-CLL (92%), nT-nB CLL (4%) and T-cell lymph-proliferative disease (4%, 10 cases). Investigations with monoclonal antibodies, especially in the T- and Null cell groups indicated that most leukemias could be placed in a modification of the lymphoid differentiation scheme described by Reinherz and Schlossman. The chronic T cell proliferations could be subdivided in two major groups; T gamma and T non gamma of which the former consisted of three separate groups, the K(iller)-, suppressor- and natural killer cell proliferations. The functional activity of the cells in chronic T cell proliferations will be dealt with in a separate communication. (no Refs)

91. CORRELATION OF CIRCULATING IMMUNE COMPLEXES AND DISEASE STATUS IN PATIENTS WITH LEUKAEMIA.

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Clin Exp Immunol; 43(1):46-53 1981

The occurrence of soluble immune complexes (IC) was investigated in 177 serum samples from 92 patients with various leukemias using the Raji cell immunoassay. In general, patients with myeloproliferative diseases had a higher incidence and higher quantities of IC than did patients with lymphoproliferative disorders. Elevated levels of IC were found in the sera of patients as follows: 17% with chronic lymphocytic leukemia (mean value of 13.1 ug/ml), 67% with acute lymphocytic leukemia (54.1 ug/ml), 65% with chronic myelocytic leukemia (86.7 ug/ml), 70% with acute myelocytic leukemia (202.5 ug/ml) and 56% with acute myelomonocytic leukemia (41.9 ug/ml). Patients in terminal blastic crisis of chronic myelocytic leukemia had the highest levels, with a mean level of 1,364.1 ug/ml. Serial samples were obtained, as available, from individual patients during the course of the disease in an attempt to relate severity with the incidence and quantity of IC. No significant correlation could be made between the occurrence or levels of IC and the presence or absence of systemic symptoms. Similarly, no correlations could be made between levels of IC and hematological parameters, infection, or therapy. However, the data does indicate a positive relationship between the levels of IC and the progressive state of the leukemia, especially, the myelocytic leukemias. (Author abstract) (27 Refs)

92. IMMUNOLOGIC PARAMETERS OF CHILDREN WITH ACUTE LEUKOSIS AFTER CESSATION OF POLYCHEMOTHERAPY UNDER REPEATED IMMUNOSTIMULATION WITH INTRADERMAL B.C.G.

Blau HJ, Eggers G, Kruse H, Schulz M, Grulich M
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Arch Geschwulstforsch; 52(2):123-128 1982

Immunologic parameters were measured in children with acute leukosis during immunostimulation with BCG after cessation of polychemotherapy. Fourteen patients, including 11 with acute lymphoblastic leukemia (ALL) and 3 with acute myeloblastic leukemia (AML) began immunostimulant therapy 6 wk after cessation of a 3-yr course of intensive polychemotherapy. BCG (0.05 ml) was injected id 2x/yr up to 5 yr and once/yr thereafter. BCG vaccination produced significant increases in peripheral-blood counts of lymphocytes (4,466 x 10(9)/liter before BCG vaccination to 7,240 x 10(9)/liter 6 wk after the third vaccination) and cells forming E-rosettes (48.5 +-21.1% before BCG treatment to 53.2 +-13.0% 6 wk after the third vaccination). Three out of 24 skin tests showed positive tuberculin reaction. A control group of patients with AML who received polychemotherapy but no BCG treatments showed no such increases. No relapse occurred in 14 patients receiving BCG during 1-3 yr observation. Among controls 19/30 were alive and 15/30 were in stable remission after an av 4 yr. Results suggest beneficial effects of BCG vaccination for patients with ALL or AML, but the patient sample was too small too draw definite conclusions. (11 Refs)

93. T-CELL GROWTH FACTOR-MEDIATED PROLIFERATION OF LYMPHOCYTES FROM A T-CHRONIC LYMPHOCYTIC LEUKAEMIA PATIENT LACKING MITOGEN AND ALLOANTIGEN RESPONSIVENESS.

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Clin Exp Immunol; 43(2):302-310 1981

Peripheral blood lymphocytes (PBL) of chronic lymphocytic leukemia of T cell origin (T-CLL), which were unresponsive to mitogens and had negligible stimulator and responder capacities in mixed lymphocyte cultures (MLC), were induced to proliferate by human T cell growth factors (TCGF). Long-term T-CLL PBL cultures were obtained in the presence of TCGF. T-CLL PBL obtained from a female patient (30 yr old) showed no 3H-thymidine (3HTdR) incorporation when stimulated with various concentrations of phytohemagglutinin (PHA), Concanavalin A, or pokeweed mitogen. The T-CLL PBL exhibited greatly reduced responder and inducer capacities (12% and 14% that of normal sheep RBC rosette-forming cells, respectively). TCGF-1 had the strongest growth-promoting activity and was used as a standard (1.0 growth-promoting unit). TCGF-1,-2, and-3 contained 0.52, 0.29, and 0.33 growth-promoting units, respectively. PHA stimulated proliferation of T-CLL cells in the presence of TCGF-1. Both TCGF-3 and-4 also induced and maintained T-CLL PBL proliferation in the presence of PHA, but at considerably lower rates than those produced in the presence of TCGF-1 and-2. In MLC, addition of TCGF-4 resulted in a four-fold increase in 3H-TdR incorporation in T-CLL PBL after stimulation with lymphocytes from a normal donor (C). Lymphocytes from donor C showed an 80-fold increase in 3H-TdR incorporation when cultured with T-CLL PBL in the presence of TCGF-4. The results indicated that the lack of response to mitogens and alloantigens of the T-CLL PBL can be attributed to the failure of these cells to produce TCGF upon activation. (36 Refs)

94. COLORECTAL CARCINOMA: EVIDENCE FOR CIRCULATING CEA-ANTI-CEA COMPLEXES (MEETING ABSTRACT).

Mavligit G, Stuckey S
University of Texas System Cancer Center, M.D. Anderson Hospital and, Tumor Institute Houston, TX
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Despite the increasing usefulness of serial plasma CEA (carcinoembryonic antigen) determination in monitoring patients with subclinical colorectal cancer, a rising CEA as measured by the conventional radioimmunassay can only be expected in approx 70% of clinically documented cases with recurrent disease. Lack of CEA production by, or release from the growing tumor, and, perhaps a modification in its antigenic moiety rendering it nonassayable were all advocated as tentative explanations. Recent studies by Staab, et al, provided strong evidence in support of the presence of circulating CEA-anti-CEA complexes. We surmised that a presplitting of such putative CEA-anti-CEA complexes in a given plasma sample must result in a higher measurable CEA. Furthermore, the eluted anti-CEA from the splitting procedure must rebind purified CEA. Plasma samples were eluted with 2.5 M MgCl2 and the IgG component was then precipitated out by Protein A. Significant increments in measurable CEA were effected in 11 of 15 patients with disseminated colorectal cancer and in five of ten patients with the Duke's C category. Complex-released IgG from a patients with a higher MgCl(2)-induced CEA increment effected a greater specific binding of I125-CEA than a similar IgG eluate from a patient with a negligible CEA increment. Our data suggest that CEA is autoimmunogenic and may result in circulating CEA-anti-CEA complex formation. (no Refs)

95. SPONTANEOUS CELL-MEDIATED CYTOTOXICITY IN PATIENTS WITH TRANSITIONAL CELL CARCINOMA OF THE URINARY BLADDER. DIFFERENCE IN EFFECTOR CELL POPULATION.

Moroz C, Lindner A, Twig S, Madgar I, Many M
Rogoff-Wellcome Medical Res. Inst., Beilinson Medical Center, Petah-Tikva, Israel
Cancer Immunol Immunother; 12(1):57-62 1981

Spontaneous lymphocyte-mediated cytotoxicity (SLMC) of peripheral blood lymphocytes (PBL) from patients (male, av age 71) with transitional cell carcinoma (TCC) of the urinary bladder was studied. SLMC of PBL against K-562 cells varied greatly, but PBL from controls and patients did not differ in cytoxic activity over a range of effector:target ratios. Following separation of effector cells into T and non-T fractions, SLMC of T lymphocytes derived from TCC patients was significantly greater than that of non-T cell populations. In controls, cytotoxic activity of non-T cells was higher than that of T cells. Repeated experiments on two TCC patients over a 1 yr period consistently showed the high SLMC of T lymphocytes. The relatively higher SLMC of T cells from TCC patients was even more profoundly exhibited when Peer cells instead of K-562 cells were targets. Neither treatment with monoclonal antibodies OKT 8 or OKT 4 and complement nor use of preparations depleted of Fc-receptor-positive cells could abolish the cytotoxicity of T cells from cancer patients. The natural killer-like T cells are thought to be a disease-related phenomenon, but their nature remains unclear. (35 Refs)

96. FUNCTIONAL STUDIES ON B CELLS IN HUMAN BONE MARROW: IN VITRO MITOGEN STIMULATION OF NORMAL AND MALIGNANT B CELLS.

Hammarstrom L, Smith CI, Pettersson D, Mellstedt H, Holm G
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Clin Exp Immunol; 43(1):157-164 1981

Using the protein A plaque assay, bone marrow cells from normal donors were shown to secrete spontaneously immunoglobulins mainly of the IgG and IgA class. After mitogenic activation, a marked increase in IgM production was observed with kinetics and cell density requirements similar to that of blood lymphocytes. In Morbus Waldenstrom patients, IgM was the predominant Ig class secreted spontaneously by bone marrow cells. The high in vitro background proliferation of these cells could be abolished by addition of the appropriate anti-idiotypic antiserum. After stimulation with mitogens, differentiation of cells within the malignant clone to immunoglobulin-secreting lymphocytes was evidenced, suggesting a retained responsive capacity of the transformed cells. (Author abstract) (27 Refs)

97. IMMUNE COMPLEXES AND HUMAN NEOPLASIA. DETECTION AND QUANTITATION OF CIRCULATING IMMUNE COMPLEXES BY THE FETAL LIVER CELL ASSAY.

Salinas FA, Wee KH, Silver HK
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Cancer Immunol Immunother; 12(1):11-19 1981

Mouse fetal liver cells (FLC) were used in development of a radioimmunoassay (RIA) for circulating immune complexes (CIC). The uptake of 125I-antihuman IgG by FLC preincubated with sera from patients with various disorders was used to quantitate CIC. Results from unfractionated aggregated human gamma globulin (AHG) and aggregates of defined size were higher with the FLC-RIA than with the Raji assay. FLC-RIA revealed elevated CIC in cancer patients as follows: malignant melanoma, 64/76, breast carcinoma, 38/77, ovarian carcinoma, 40/86, lung carcinoma, 5/17, colon carcinoma, 9/12, and testicular carcinoma, 3/4. The FLC/RIA and Rai tests were compared using 76 serum samples; results were generally in agreement, but FLC-RIA was more sensitive in quantitation of CIC for fewer and smaller immune complexes, conditions in which the Raji assay is reportedly relatively insensitive. (50 Refs)

98. THE VALUE OF A NEW B-CELL SPECIFIC MONOCLONAL ANTIBODY IN COMBINATION WITH CONVENTIONAL IMMUNOLOGIC MARKERS FOR TYPING OF MALIGNANT NHL (MEETING ABSTRACT).

Obrecht JP, Christen D, Forster HK, Gudat FG
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UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Results obtained by a new B-specific monoclonal antibody were compared to those of conventional marker analysis (rosette formation with sheep and mouse RBC, sIg, Fc-receptor) in 32 patients (pat) with malignant Non-Hodgkin's lymphoma (NHL). This monoclonal antibody, anti-Y29/55, was produced by fusion between a mouse myeloma cell line and splenocytes of a mouse immunized to peripheral blood lymph ocytes (PBL) of a patient with untreated chronic lymphocytic leukemia (CLL). Previous experiments had shown that this antibody reacted with normal sessile B-lymphocytes but not with nonneoplastic B-cells circulating in blood. The following results were obtained by conventional marker typing: 15 CLL were of the B-cell type. Eleven NHL (5 lymphocytic poorly differentiated, 2 lymphohistocytic, 3 histiocytic and 1 Burkitt's lymphoma) were positve for B-markers. Four NHL (2 lymphocytic poorly differentiated, 1 lymphohistiocytic, 1 histiocytic) were of the T-cell type. Two histiocytic NHL did not express B- or T-markers. The monoclonal antibody detected all B-cell lymphomas in blood and/or tissue. Additionally 1 of the histiocytic lymphomas which was negative to conventional markers reacted with anti-Y29/55. The antibody did not react with T-cell lymphomas. (no Refs)

99. ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY IN HUMAN CANCER: CHARACTERIZATION OF PATIENT LEUKOCYTE ACTIVITY AND TREATMENT EFFECTS.

Hersh EM, Murphy SG, Gutterman JU, Morgan J, Quesada J, Zander A, Stewart D
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 49(2):251-260 1982

Antibody-dependent cell-mediated cytotoxicity (ADCC), mediated by peripheral blood Hypaque-Ficoll separated mononuclear cells, was studied in humans using chicken erythrocytes (CRBC) incubated in a 1:1,200 dilution of rabbit anti-CRBC and human B erythrocytes (HRBC) incubated in a 1:20 dilution of isoantibody. At the optimal target effector ratio of 3:1, ADCC to both CRBC and HRBC was significantly higher than normal in 27 lung cancer, 18 malignant melanoma, and 7 colon cancer patients, but not in 20 breast cancer patients. Chemotherapy (single-agent or combination) in 12 patients did not affect ADCC in vitro but significantly suppressed ADCC to both targets after only 4 or 5 days of therapy in vivo (ADCC to CRBC, 47.4 to 24.1% lysis: ADCC to HRBC, 48.1 to 16.3% lysis). Immunotherapy with intravenous (IV) Corynebacterium parvum or IV methanol extraction residue of BCG (MER) boosted ADCC to both targets within 4 to 7 days of the first dose. It was found that ADCC to HRBC but not to CRBC was completely absent in three cases of active hairy cell leukemia but was present in two cases in remission. The ADCC to HRBC showed an age-dependent increase in both the 51 normal subject and the cancer patients. This was not observed for ADCC to CRBC. The ADCC to CRBC was mediated mainly by an Fc-receptor-positive, nonadherent, small lymphocyte, and ADCC to HRBC was mediated entirely by an adherent monocyte. The ADCC did not correlate significantly with the H3 thymidine incorporation of peripheral blood mononuclear cells, cultured without stimulation for either 1 or 7 days. It also did not correlate with the number of residual granulocytes in the mononuclear cell suspensions. Measurement of ADCC is a useful method of characterizing host defense in malignant disease and its modification by therapy. (Author abstract) (48 Refs)

REVIEWS

100. EMERGING IMMUNOLOGIC APPROACHES TO TREATMENT OF NEOPLASTIC DISEASES.

Olsson L, Mathe G

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Recent Results Cancer Res; 80:334-337 1982

Recent research on the immunobiology of the tumor-host relationship has demonstrated that nonspecific cellular immune reactions, like natural killer cells and cytotoxic autoreactive cells, may be far more potent antineoplastic mechanisms than specific T lymphocyte cytotoxicity. The hybridoma technique, making it possible to raise monoclonal antibodies against predefined antigens, has rendered passive immunotherapy more attractive. It is suggested that the combination of nonspecific cellular immune reactions with monoclonal antibodies may be a highly efficient antineoplastic therapy for minimal residual disease. (Author abstract) (19 Refs)

101. HYBRIDOMAS: A NEW DIMENSION IN BIOLOGICAL ANALYSES.

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In Vitro; 17(12):1036-1050 1981

Since the first report of hybridomas producing monoclonal antibodies by Kohler and Milstein in 1975, this technique has spread to nearly all areas of biological, biochemical, and biomedical research. Watching the use of these methods spread from immunologists to cell biologists, developmental biologists, biochemists and to other biological disciplines and observing the nearly logarithmic increase in publications using these reagents has been in itself fascinating and informative. An overview of the development of this technology and its applications is presented including the use of monoclonal antibodies to study cell surface molecules, differentiation antigens, receptors, and histocompatibility antigens. The use of these antibodies to analyze microorganisms and parasitic antigens as well as their use in the genetic analysis of human cell surface antigens and the detection of polymorphic variation in enzymes and other proteins is discussed. Examples of the application of monoclonal reagents to the study of tumor cell biology including the labeling of metastatic tumor cells and the detection of cell surface molecules implicated in the regulation of growth control and cell division are provided. (Author abstract) (232 Refs)

102. UTILIZATION OF MONOCLONAL ANTIBODIES IN THE TREATMENT OF LEUKEMIA AND LYMPHOMA.

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Blood; 59(1):1-11 1982

The generation of murine monoclonal antibodies reactive with human leukemia and lymphoma cells has recently led to clinical trials that have begun to evaluate the use of these reagents in the treatment of various leukemias and lymphomas. Several of these studies have demonstrated that infusion of monoclonal antibody can cause the rapid and specific clearance of leukemic cells from the peripheral blood. Intravenously administered antibody also rapidly binds to bone marrow lymphoblasts, and in one instance, has resulted in the partial regression of tumor cell infiltrates in lymph nodes and skin. Unfortunately, clinically significant responses have not in general been achieved, but these clinical studies have identified specific factors that result in the development of resistance to antibody-mediated lysis in vivo. These factors include the presence of circulating antigen, antigenic modulation, reactivity of monoclonal antibody with normal cells, immune response to murine antibody, and the inefficiency of natural immune effector mechanisms. Current research is now being directed towards developing methods to circumvent each of these obstacles. Future clinical studies utilizing antibodies in vitro or with different specificity may demonstrate greater therapeutic efficacy. In addition, monoclonal antibodies can be used as carriers of other cytotoxic agents and in conjunction with other agents that will reduce the total tumor load. Monoclonal antibodies represent new and powerful reagents that may in the near future become an additional therapeutic modality for patients with malignant disease. (Author abstract) (100 Refs)

103. PRESENT STATUS AND FUTURE PROSPECTS FOR THE HYBRIDOMA TECHNOLOGY.

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In Vitro; 17(12):1072-1077 1981

A somatic cell genetic technique has recently been developed that makes it possible to obtain very large amounts of homogeneous antibodies and to replenish the supply of the exact same antibodies whenever they are needed. This hybridoma technology has already contributed to major scientific advances and will surely improve the diagnosis and treatment of many diseases. Because the technology itself is relatively simple and inexpensive, it has captured the attention of basic scientists, clinicians, and industrial managers and investors. (Author abstract) (30 Refs)

104. METHODS IN ENZYMOLOGY: INTERFERONS, PART A.

Pestka S
Roche Inst. Molecular Biology, Nutley, NJ
Methods Enzymol 78: 632 pp., 1981.

Induction, production, purification, characterization, assay of interferon, and preparation of viral and nonviral inducers of interferon are described. Definition, classification, standardization of interferon assay, and standard media are presented. Methods for purifying interferons, focusing on fibroblast and leukocyte interferons, are discussed. Reverse and normal phas high-performance liquid chromatography is applied in the purification of interferon. Amino acid composition, peptide maps, and some interferon amino acid sequences have been determined. Complete amino acid sequences of human fibroblast and several leukocyte interferons are known. Fibroblast and leukocyte interferons have been expressed in bacteria. Recombinant leukocyte interferon has been purified to homogeneity and has been in clinical trial for several months. The isolation of monoclonal antibodies to leukocyte interferon has been instrumental in the effective purification of recombinant human leukocyte interferon and in the development of convenient immunoassays for the detection of leukocyte interferon. Crystals of recombinant interferon have been obtained; elucidation of their tertiary structure by x-ray crystallography is expected. Interferon inducers, classification, and preparation with focus on commercial sources are discussed. (1136 Refs)

105. INTERFERONS AND CANCER: THE END OF THE BEGINNING OR THE BEGINNING OF THE END.

Priestman TJ
No affiliation given
Clin Oncol; 7(4):271-274 1981

Human interferon (IFN) and its role in cancer therapy are reviewed. IFN may act directly as a growth inhibitor by arresting cell division or indirectly through the immune system. IFN has been shown to stimulate lymphocyte cytotoxicity and enhance macrophage and natural killer cell activity. Three human IFN, alpha, beta, and gamma, have been identified. Alpha IFN are produced by WBC in response to challenge with virus; at least eight alpha IFN polypeptides with mol wt between 18,000 and 25,000 exist. Beta IFN are produced by fibroblasts stimulated by viral infections. Lymphocytes exposed to some immunostimulants can produce gamma IFN. Results of dose-toxicity studies with the genetically engineered subtype IFN alpha2 are described. The overall response rates for IFN alpha2 treatment of cancers where data are available on greater than 15 patients are: breast carcinoma (35%), multiple myeloma (40%), non-Hodgkin's lymphoma (50%), malignant melanoma (7%), and large cell cancer (0). Most of these patients had advanced recurrent tumors. In a non-randomized study of patients with early osteogenic sarcoma, the 3-yr survival rates for IFN-treated and control patients were 69% and 34%, respectively. Although the results with IFN appear to be discouraging, conclusions should not be drawn since the range of tumors evaluated to date is small, only im administration of IFN has been studied, and no clinical series has determined the role of IFN in combination with existing cytotoxic agents. (19 Refs)

106. INTERFERONS AND INTERFERON INDUCERS: DEVELOPMENT OF CLINICAL USEFULNESS AND THERAPEUTIC PROMISE.

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Drugs; 23(1/2):37-55 1982

Studies concerning applications of interferon (IF) and IF-inducers in humans are discussed. General properties, pharmacokinetics, indications for use, and adverse reactions of IF are reviewed. Therapeutic trials discussed include measurement of efficacy, local and systemic administration of IF focusing on systemic administration against herpesviruses, hepatitis B virus infections, and antitumor applications. Therapeutic trials with various IF-inducers are discussed: viral inducers, pyran copolymer and tilorone, and polyinosinic-polycytidylic acid. (127 Refs)

107. ADJUVANT THERAPY FOR MALIGNANT MELANOMA.

Kaiser LR, Burk MW, Morton DL
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Surg Clin North Am; 61(6):1249-1257 1981

Use of immunotherapy (IT), chemotherapy (CT), combined chemo- and immunotherapy (CIT), and radiotherapy (RT) as adjuvant therapy (AT) for malignant melanoma is reviewed. IT is based on immune manipulation allowing for selective attack and destruction of small numbers of tumor cells on a systemic level, without a significant increase in toxicity. Clinical studies have confirmed the susceptibility of melanoma to immune attack. Most studies have used BCG for nonspecific AT; specific active IT of x-irradiated neuraminidase-treated melanoma cells has been combined with BCG given sc. Systemic CT for melanoma has been limited to dimethyl triazeno imidazole carboxamide (DTIC). In one study, toxicity apparent in all patients included nausea and vomiting, but no deaths occurred from drug toxicity. Attempts have been made to increase the adjuvant effect of CT by combining it with IT. DTIC as a single agent and with BCG has been used in the studies comparing CT with CIT. CIT is apparently significantly better than DTIC alone in the prevention of early recurrent disease. In studies of RT, data appeared at first to show enhanced survival and an increased disease-free interval in irradiated groups, but on re-examination the differences were shown to result from inter-group imbalances in age and nodal status. (27 Refs)

108. INTERFERON: IMMUNOBIOLOGY AND CLINICAL SIGNIFICANCE.

Stiehm ER, Kronenberg LH, Rosenblatt HM, Bryson Y, Merigan TC
Dept. Pediatrics, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
Ann Intern Med; 96(1):80-93 1982

Interferons are proteins elaborated by infected cells that protect noninfected cells from viral infection. These proteins produce a temporary 'antiviral state' by altering nucleotide metabolism and cytoplasmic enzyme induction. Interferons appear early after viral infection locally and systematically to limit spread of viral infection; they also affect cell differentiation, growth, surface antigen expres sion, morphologic findings, and immunoregulation. Several human disorders have diminished interferon production. Newborns have normal interferon alpha but deficient interferon gamma production. Infants with congenital infections may also have defects in interferon production. Immunosuppressed patients receiving transplants (marrow, heart, or kidney) have diminished interferon production, particularly immediately after transplant. Deficiencies of interferon have also been noted in Down's syndrome, cellular immunodeficiencies, uremia, malnutrition, and hematopoietic malignancy. Leukocyte interferon has been of therapeutic value in herpes zoster infections, in patients with cancer, and in patients with hepatitis B infection. Interferon has not been proved to help children with congenital cytomegalovirus or rubella. Interferon can shrink lymphoid tumors, particularly non-Hodgkin's lymphoma. (Author abstract) (160 Refs)

109. CANCER IMMUNOTHERAPY: SOME CRITICAL COMMENTS REGARDING IMMUNOLOGICAL MONITORING.

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Int J Immunopharmacol; 3(4):339-348 1981

Determination of pretreatment immune status and measurement of drug-related changes in immune response during cancer chemotherapy with levemisole (LV) are discussed. Prior cancer sensitization may be a prerequisite for successful LV treatment and can be determined by various direct and indirect in vivo and in vitro tests. Detection of pretreatment defects in immunologic expression is discussed under the following headings: energy and lymphocytes, monocytes/macrophages, B-lymphocytes, miscellaneous humoral factors, tumor load, suppressor cells, in vitro modulation of functions, and mononuclear cell enumeration. Delayed-type hypersensitivity skin reactions, phytohemagglutinin-induced blast formation, Fe-receptor-bearing lymphocytes, mixed lymphocyte culture reactivity, 'null' cell numbers, and monocyte chemotaxis may show changes during LV therapy and may serve as prognostic indicators. LV may enhance tumor-specific cell-mediated immunity and prolong the presence of high levels of antitumor membrane IgG antibodies in sera of patients receiving tumor vaccines. Exogenous factors that could interfere with desirable immune changes, including surgery, radiotherapy and chemotherapy, are discussed. Timing of LV therapy is discussed in relation to timing of conventional treatment and to the last dose of LV; duration of LV treatment; time as a chronobiological variable; and time as related to delayed-type hypersensitivity skin testing. (57 Refs)

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CLINICAL CANCER IMMUNOLOGY AND IMMUNOTHERAPY

SERIES CT06 No. 82/07

JULY, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

CLINICAL TRIALS

1. LOWER RELAPSE RATES AFTER NEIGHBOURHOOD INJECTION OF CORYNEBACTERIUM PARVUM IN OPERABLE CERVIX CARCINOMA.

Mignot MH, Lens JW, Drexhage HA, Von Blomberg BM, Flier VD, Oort J, Stolk JG
Dept. Obstetrics and Gynecology, Free Univ. Hosp., Amsterdam, The Netherlands
Br J Cancer; 44(6):856-862 1981

The effect of adjuvant immunotherapy with a single neighborhood injection of 2 mg C parvum (CP) was investigated in a randomized study involving 43 patients with carcinoma of the c ervix uteri, all of whom were treated by radical surgery. All patients had carcinoma confined to the cervix, the upper part of the vagina or the parametrial region. When the malignancy had spread to the parametrial region, additional postoperative radiotherapy was given. Twenty two patients received immunotherapy 10 days before surgery, whereas the remaining 21 control patients received no immune stimulation. Only minor side effects of CP were encountered. Follow-up shows a relapse rate of 5% in the CP treated group and of 29% in the controls (p less than 0.05). A further 15 patients with more advanced malignancies were added to our studies. In these, CP stimulation had no effect on relapse rates, but the relapse-free intervals were longer after immune stimulation: control 3.5 mo (mean) +-1.5 (sd), CP 13.0 mo +-7.0 (p less than 0.05). The number of peripheral T cells and the ability to become sensitized to DNCB were increased after CP stimulation. A decrease was found in the number of blood monocytes and the number of monocytes capable of transforming into active macrophages, indicating a possible sequestration of these cells in the tissues. (Author abstract) (40 Refs)

2. RESULTS OF CHEMOIMMUNE PROPHYLAXIS OF SUPERFICIAL BLADDER CARCINOMA.

Adolphs HD, Helpap B
Urologische Universitatsklinik, D-5300 Bonn-Venusberg, W. Germany
Urologe [A]; 21(1):29-33 1982

Forty-one patients (37-79 yr old) with solitary or multiple urothelial carcinoma of the bladder (CB) in Stages PA or P1 were treated with chemoimmune prophylaxis (CIP) after complete surgical resection of tumor. Cyclophosphamide (CP: 700 mg/square meter, iv) was injected 2 wk after tumor resection. BCG was instilled in the bladder 1 x/wk for 6 wk beginning 2 wk after CP injection. BCG was retained in the bladder for at least 1 hr. Percutaneous BCG immunization was administered to the upper thigh simultaneously with each BCG instillation. Results in the treated group were compared with results in 65 historical control cases. The recurrence rate for controls was 49% during 4 yr after resection. Tumors recurred in 5/41 patients receiving CIP. The difference between recurrence rates for the CIP group and controls was greatest during the first 6 mo after resection. Side effects of treatment were tolerable and included dysuria (35/41 patients), pollakiuria (25/41 patients), and fever (13/41 patients). One case each of epididymitis and allergic skin reaction to BCG occurred. All side effects were controlled by treatment of symptoms. Suspected endoscopic findings required a second resection in four cases; no tumor recurrence was confirmed histologically. Results indicate that CIP is effective in preventing recurrence of CB and in lengthening the tumor-free interval in those patients suffering recurrence. (50 Refs) (In GER)

SYNTHETIC IMMUNOTHERAPEUTIC AGENTS

3. INFLUENCE OF THE IMMUNOMODULATING COMPOUND BM 12.531 (AZIMEXONE) ON RADIORESISTANCE AND GRANULOPOIETIC COLONY FORMING UNITS IN MICE.

Gassel WD, Laukel H, Braun R, Werner T, Bicker U
(c/o Bicker) Dept. Immunostimulation and Cancer Res., Boehringer Mannheim GmbH, Sandhofer Strasse 116, D-6800 Mannheim 31, W. Germany
Exp Pathol; 20(2):105-107 1981

BM 12.531 (azimexone) increases the survival of mice exposed to 650 rad. Levamisole, isoprenosine or aristolochia acid have no effects in this system. After administration of 25 mg/kg azimexone to C57 Bl/6-mice, a statistically significant increase in CFUc was found. This increase in CFUc may explain the radioprotective effect of azimexone. (Author abstract) (12 Refs)

INTERFERON

4. HUMAN INTERFERONS ALPHA AND BETA INHIBIT T-CELL-DEPENDENT AND STIMULATE T-CELL-INDEPENDENT MITOGENESIS AND NATURAL CYTOTOXICITY: RELATIONSHIP TO CHROMOSOME 21.

Matheson DS, Green B, Tan YH
Div. Pediatrics and Medical Biochemistry, Univ. Calgary, Calgary, Canada
Cell Immunol; 65(2):366-372 1981

The effects of purified human interferons, interferon-alpha and interferon-beta, on immunocompetent cells were compared. Both types of interferon inhibited blast transformation to the T-cell-dependent mitogens phytohemagglutinin, concanavalin A and pokeweed mitogen with IFN-alpha being more potent than IFN-beta. B-Cell mitogenesis induced by Staphylococcus Cowan I was enhanced by both IFN preparations with IFN-beta being more potent than IFN-alpha. Both types of IFN enhanced natural killer cell activity with differences in the dose-response curves. The expression of the IFN-induced modulation of the mitogenic responses was shown to be associated with human chromosome 21. No such association could be demonstrated for the effect of IFN on natural killer cell activity. (Author abstract) (31 Refs)

5. EFFECT OF INTERFERON ON THE INHIBITION OF THE GROWTH OF MALIGNANT CELLS BY HUMAN PERIPHERAL LEUKOCYTES. III. INFLUENCE OF SYSTEMIC ADMINISTRATION.

Kita M, Imanishi J, Kishida T
Dept. Microbiology, Medical Univ. Kyoto Prefecture, Kawaramachi-Hirokoji, Kamikyo-ku, Kyoto 602, Japan
C R Soc Biol (Paris); 175(6):904-909 1981

Effects of human WBC interferon (IFN) on spontaneous tumor cell growth inhibition (STCI) by human peripheral lymphocytes and on natural killer (NK) activity was studied in cultures of 10(5) HeLa cells and in 19 patients with malignant tumors (3 cervical, 6 lung, 4 tongue, 1 breast, 1 stomach, and 4 brain tumors) and in 11 patients with chronic type B hepatitis. Less STCI was noted in patients with cancer or hepatitis than in normal subjects. In vitro responses to IFN were the same for healthy subjects and patients. No significant increase in STCI was observed during the 24 hr after IFN administration, while N K activity was augmented. When IFN (10(6) IU during wk 1, 0.5 x 10(6) wk 2, 0.2 x 10(6) wk 3, and 10(5) wk 4) was administered systemically to the cancer and hepatitis patients, STCI gradually increased while NK activity was increased only after 10(6) IU and 0.5 x 10(6) IU of IFN were administered. The results indicated that systemic administration of IFN to patients with cancer or chronic hepatitis augmented the inhibition of STCI by human peripheral lymphocytes as well as NK activity. A difference between NK cells and effector cells for STCI was demonstrated. (4 Refs) (In FRE)

6. ACTIVATION OF NATURAL CYTOTOXICITY OF HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS BY INTERFERON: A KINETIC STUDY AND COMPARISON OF DIFFERENT INTERFERON TYPES.

Claeys H, Van Damme J, De Ley M, Vermylen C, Billiau A
Blood Transfusion Center, O. L.Vrouwstraat 42, B-3000 Leuven, Belgium
Br J Haematol; 50(1):85-94 1982

Overnight incubation of human peripheral blood mononuclear (PBMN) cells with leukocyte interferon (leucocyte IFN) resulted in a two-five-fold increase in natural cytotoxicity (NC) against the erythroleukemic cell line K562. Fibroblast IFN, purified to homogeneity by zinc-chelate chromatography, stimulated NC to the same extent, while partially purified immune IFN was about twice as active. Upon gel filtration of immune IFN, NC stimulating and antiviral activity co-eluted. Treatment of PBMN cells with ammonium chloride buffer (AmCl) abrogated NC nearly completely. Incubation of AmCl-treated cells with leukocyte IFN resulted in a partial regeneration of NC. Kinetic studies revealed that this regeneration required only a short exposure to IFN followed by a longer incubation period. The data are interpreted as indicating that in the process of NC activation IFN mainly acts as a trigger for precursor cells to mature into cells with NC. (Author abstract) (26 Refs)

7. INTERFERON-INDUCED CHANGES IN THE MONOCYTE MEMBRANE: INHIBITION BY RETINOL AND RETINOIC ACID.

Rhodes J, Stokes P
Immunology Div., Addenbrooke's Hosp., Hills Road, Cambridge, CB2 2QQ, England
Immunology; 45(3):531-536 1982

The effects of human interferon-beta on human peripheral blood monocyte function were examined in vitro. Interferon-beta was shown to increase substantially the expression of both Fcgamma receptors and HLA-DR antigens defined by monoclonal antibody. Retinol and retinoic acid were found to be antagonistic to these effects of interferon and physiological concentrations were sufficient to inhibit changes in the monocyte membrane induced by relatively high concentrations of interferon. (Author abstract) (31 Refs)

8. ALLOREACTIVE CYTOTOXICITY OF INTERFERON-TRIGGERED HUMAN LYMPHOCYTES DETECTED WITH TUMOR BIOPSY TARGETS.

Vanky F, Klein E
Dept. Tumor Biology, Karolinska Institutet, S-10401 Stockholm 60, Sweden
Immunogenetics; 15(1):31-39 1982

Interferon activation of lymphocytes produces lytic potential against allogeneic but not against autologous biopsy-derived tumor cells. This effect was seen when targets isolated from solid tumors were used directly without cultivation in vitro. The hypothesis that the lytic effect was due to activation of alloreactive cells was tested in the cold target competition assay. The results substantiated our assumption because they showed that in a given lymphocyte population separate sets act on allogenic tumor cells derived from different individuals. In addition PHA blasts from the target-cell donor but not from unrelated individuals also inhibited the lysis. The system we use is operationally an NK assay in which antigen (MHC)-recognizing lymphocytes seem to function. Since antigen recognition is a property of the T subset, the conceptual dualism in the classification of NK and CTL effects should be modified. (Author abstract) (25 Refs)

9. CELLULAR ORIGIN AND INTERACTIONS INVOLVED IN GAMMA-INTERFERON PRODUCTION INDUCED BY OKT3 MONOCLONAL ANTIBODY.

Chang TW, Testa D, Kung PC, Perry L, Dreskin HJ, Goldstein G
Immunobiology Div., Ortho Pharmaceutical Corp., Raritan, NJ, 08869
J Immunol; 128(2):585-589 1982

OKT3 monoclonal antibody, a human T cell mitogen, induced interferon production by cultured mononuclear cells at 10(-11) M concentrations. Interferon was secreted only under conditions wherein OKT3 was mitogenic, and production was correlated with cell proliferation. Thus, like mitogenesis, interferon secretion reached a peak 3 days after OKT3 stimulation, was inhibited by a factor(s) in human serum, and required 1,000x higher concentrations of Fab and F(ab')2 fragments of OKT3 for induction. The interferon was most likely of 'gamma' (immune) type, because pH 2 and 56 C treatments denatured it, whereas anti-alpha or -beta interferon antibodies did not. Mononuclear cells were fractionated into subpopulations that contained OKT4+ cells (helper/inducer T cells), OKT8+ cells (cytotoxic/suppressor T cells), and OKM1+ cells (monocytes) by combining sheep red blood cell rosetting and complement-mediated lysis using monoclonal antibodies against specific cell types. Both OKT4+ and OKT8+ cells proliferated upon OKT3 stimulation with the absolute requirement of OKM1+ cells. However, OKT4+ cells plus OKM1+ cells were necessary for the secretion of interferon. Studies with selective pretreatments with mitomycin C suggested that gamma-interferon was secreted by the OKT4+ cells and that the OKM1+ population subserved an accessory function. (Author abstract) (27 Refs)

10. EFFECT OF THYMOSIN FRACTION 5 ON THE PRODUCTION OF MURINE GAMMA INTERFERON.

Sonnenfeld G, Mansfield JM
Dept. Microbiology and Immunology, Univ. Louisville, Health Sciences Center, Louisville, KY, 40292
Immunopharmacology; 4(1):87-93 1982

Interactions between thymosin fraction 5 (TF5) and interferon (IF) in an immunoregulatory circuit were studied in randomly bred female Swiss/Webster mice 4-to 6-wk-old. Each mouse received 120 ug TF5 ip. Thirty min later iv injection of 10 ug polyriboinosinic-polyribocytidylic acid (polyrI:rC) was administered. No effect on induction of IF was observed. Additional treatment with 120 ug TF5 prior to exposure to polyrI:rC had no effect on IF induction. Infection with Mycobacterium bovis strain BCG and injection of TF5 prior to challenge with 50 mg tuberculin (TB) had no effect on gamma IF production. Ip administration of TF5 21 days after sensitization and again after 24 hr, followed 30 min later by iv challenge with TB, depressed production of gamma IF. No effect on gamma production was observed when only one dose of TF5 was administered to BCG-sensitized mice 24 hr prior to gamma IF induction with TB. At least two injections of TF5 are required to influence gamma IF production. Treatment of gamma IF with an antiserum directed against alpha/beta IF had no significant effect on the antiviral titer of the sample. Treatment of mice with kidney fraction 5 or with bovine serum albumin had no effect on the production of gamma IF. Groups of sensitized and untreated mice received one or two dosages of TF5. Unsensitized mice were then challenged with TB. No induction of IF as result of TF5 treatment was observed. (21 Refs)

11. GAMMA INTERFERON PRODUCTION BY COMBINATIONS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES, MONOCYTES, AND CULTURED MACROPHAGES.

Arbeit RD, Leary PL, Levin MJ

Infectious Diseases Res., Medical Service, Veterans Admin. Medical Center, Boston, MA, 02130

Infect Immun; 35(2):383-390 1982

Mitogen-induced interferon (IFN) production was studied using human peripheral blood mononuclear cells and subpopulations of lymphocytes, monocytes, and cultured macrophages. Cell populations were prepared in suspension to permit quantitative analysis of the interactions among different cell types. After stimulation by staphylococcal enterotoxin A, nylon column-purified lymphocytes produced only 5% as much IFN as the peripheral blood mononuclear cells from which they were prepared. When lymphocytes were supplemented with as little as 2% monocytes, IFN production increased two- to eightfold; with the addition of up to 20% monocytes, IFN production increased further, to levels approximating those of peripheral blood mononuclear cells. Monocytes alone produced no or very little IFN. Macrophages were derived from monocytes by culturing in vitro for 7 days. The addition of 2 to 5% autologous macrophages augmented IFN production to the same extent as 2 to 5% monocytes. However, more macrophages consistently resulted in less, rather than more, IFN, so that lymphocytes with 20% monocytes produced three- to eightfold more IFN than did lymphocytes with 20% macrophages. Thus, whereas the addition of monocytes over a broad dose-response range (2 to 20%) progressively augmented IFN production, macrophages showed an optimal effect at 2 to 5%, with higher percentages being inhibitory. The IFN induced by stimulation with staphylococcal enterotoxin A was characterized as IFN-gamma by its resistance to neutralization by antibody to IFN-alpha and its inability to induce antiviral protection in embryonic bovine trachea cells. (Author abstract) (23 Refs)

12. A WHOLE-BLOOD TECHNIQUE FOR TESTING PRODUCTION OF HUMAN INTERFERON BY LEUKOCYTES.

Kirchner H, Kleinicke C, Digel W

Institut fur Virusforschung, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany

J Immunol Methods; 48(2):213-219 1982

Interferon production was studied in mixtures of whole blood of healthy adults with tissue culture medium. There was no need to supplement the system with additional foreign serum and even the autologous serum could be removed by washing in serum-free medium without impairment of interferon production. Heparinized blood samples could be stored in the refrigerator overnight before performing the assay. In this test, production of interferon gamma was observed in response to phytohemagglutinin, concanavalin A, pokeweed mitogen, staphylococcal enterotoxin A, and to OKT-3, a monoclonal anti-T cell antibody. Production of interferon alpha was observed when viruses were used as inducers. Our experiments show that in the whole-blood assay the responses to several inducers of different types of interferons may be readily monitored under serum-free conditions. We believe that this test will be of value for testing large numbers of normal individuals (for investigations of the genetics of interferon production) or of patients with a variety of diseases. (Author abstract) (11 Refs)

13. SPONTANEOUS PRODUCTION OF GAMMA INTERFERON AND INDUCED PRODUCTION OF BETA INTERFERON BY HUMAN T-LYMPHOBLASTOID CELL LINES.

Morris AG, Morser J, Meager A

Dept. Biological Sciences, Univ. Warwick, Coventry CV4 7AL, England

Infect Immun; 35(2):533-536 1982

Two human T-lymphoblastoid cell lines, CCRF/CEM and Molt 4, produced beta interferon (IFN-beta) upon infection with Sendai virus. Molt 4, but not CCRF/CEM, spontaneously produced up to 300 U of IFN-gamma per ml, apparently not contaminated with IFN-alpha or -beta. Phytohemagglutinin, a T-cell mitogen, did not stimulate IFN production in these lines. A third T-lymphoblastoid line, CCRF/HSB2, produced no IFN either spontaneously or after infection with Sendai virus or treatment with phytohemagglutinin. The Molt 4 cells contained an mRNA which could be translated by oocytes to give IFN-gamma. Molt 4 cells therefore provide a convenient source of human IFN-gamma and its mRNA for experimental purposes. (Author abstract) (19 Refs)

14. EXPRESSION OF HUMAN IMMUNE INTERFERON CDNA IN E. COLI AND MONKEY CELLS.

Gray PW, Leung DW, Pennica D, Yelverton E, Najarian R, Simonsen CC, Derynck R, Sherwood PJ, Wallace DM, Berger SL, Levinson AD, Goeddel DV

Dept. Molecular Biology, Genentech, Inc., 460 Point San Bruno Blvd., South San Francisco, CA, 94080

Nature; 295(5849):503-508 1982

A cDNA sequence coding for human immune interferon (IFN-gamma) has been identified in a cDNA library prepared from gel-fractionated IFN-gamma mRNA. The DNA sequence codes for a polypeptide of 166 amino acids, 20 of which could constitute a signal peptide. The polypeptide produced through expression of this DNA sequence in Escherichia coli or cultured monkey cells had properties characteristic of authentic human IFN-gamma. (Author abstract) (74 Refs)

15. A RADIOIMMUNOASSAY OF HUMAN LEUKOCYTE INTERFERON USING PROTEIN A-CONTAINING STAPHYLOCOCCUS AUREUS.

Daubas P, Mogensen E
Laboratoire d'Oncologie Virale, Institut de Recherches Scientifiques sur le Cancer, BP 8, 94802 Villejuif, France
J Immunol Methods; 48(1):1-12 1982

We report the establishment of a radioimmune assay for human alpha-interferon using highly purified alpha-interferon labeled with iodine-125, a purified rabbit immunoglobulin directed against human interferon and the Cowan strain of Staphylococcus aureus. Radiolabeling conditions used do not change the antigenicity of interferon molecules. The regression of counts bound upon log dose was found to be linear down to 10 units/ml of alpha-interferon (6-7 x 10(-12) M). This assay was specific for alpha-interferons derived from human peripheral blood leukocytes and from a continuous line of lymphoblastoid cells. No cross-reaction was found with either human beta-interferon or murine interferon. Neither human serum nor plasma interfered with the assay. Correlation between biological assay and radioimmune assay was found to be significant. (Author abstract) (25 Refs)

16. CHARACTERIZATION OF IMMUNE TYPE INTERFERON (IFNGAMMA)-INDUCED CYTOPLASMIC PROTEIN KINASE ACTIVITY IN MOUSE L CELLS.

Ohtsuki K, Torres BA, Johnson HM
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Biochem Biophys Res Commun; 104(2):422-429 1981

Mouse immune interferon (IFN-gamma) induced double-stranded RNA-dependent protein kinase activity in the cytoplasmic fraction of mouse L cells, measured by histone phosphorylation with (gamma-32P)ATP. The protein kinase activity was separated by column chromatography into three fractions of 100,000, 70,000, and 70,000 dalton mol wt. The fractions differed in Mg++ and Ca++ requirements, cyclic AMP activation, N-ethylmaleimide inhibition effect, and substrate requirements. (15 Refs)

INTERFERON INDUCING AGENTS

17. POLYRIBOINOSINIC-POLYRIBOCYTIDYLIC ACID-POLY-L-LYSINE COMPLEX [POLY(ICL)] WITHOUT CARBOXYMETHYLCELLULOSE (CMC): A NEW PRIMATE-EFFECTIVE INTERFERON INDUCER.

Riley FL, Morin ML, Lvovsky E, Stephens EE, Levy HB
(c/o Levy), NIH, NIAID, OSD, Building 5, Room B1-32, Bethesda, MD, 20205
Proc Soc Exp Biol Med; 169(2):183-188 1982

Studies were carried out to determine if a nuclease-resistant interferon-inducing complex could be formulated from polyriboinosinic-polyribocytidylic acid [poly(I)-poly(C)] and poly-L-lysine in the absence of carboxymethylcellulose. The technique described makes possible the preparation of polyriboinosinic-polyribocytidylic acid-poly-L-lysine [poly(ICL)] complexes of much higher concentrations than previously obtainable. Preparations of poly(I)-poly(C) stabilized with two different amounts of poly-L-lysine without carboxymethylcellulose are described. A poly(ICL) complex with a ratio for PO4:NH2 of 1:0.77 is the more resistant to hydrolysis by ribonuclease-A and is an effective inducer of interferon in monkeys. As the amount of poly-L-lysine increased, resistance to hydrolysis by ribonuclease increased and primate interferon-inducing capacity increased. However, the Tm decreased as the amount of poly-L-lysine increased, suggesting that resistance to hydrolysis is a more important predictor of the ability to induce interferon in primates than is thermodynamic stability. Poly(ICL) was less toxic in mice than was poly(I)-poly(C) with poly-L-lysine in 0.5% carboxymethylcellulose, as determined by LD50 values. (17 Refs)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

18. ACTIVE SPECIFIC IMMUNOTHERAPY OF ESTABLISHED MICROMETASTASES WITH BCG PLUS TUMOR CELL VACCINES: EFFECTIVE TREATMENT OF BCG SIDE EFFECTS WITH ISONIAZID.

Hanna MG, Pollack VA, Peters LC, Hoover HC
Cancer Metastasis and Treatment Lab., NCI-Frederick Cancer Res. Facility, P. O. Box B, Frederick, MD, 21701
Cancer; 49(4):659-664 1982

Intradermal vaccinations with BCG and viable but nontumorigenic syngeneic hepatocarcinoma cell vaccines were used successfully to treat micrometastatic disease experimentally induced in inbred guinea pigs at 100x the minimal lethal dose. Several complications have been associated with the use of viable BCG organisms is the treatment of cancer patients and, in this animal model, intradermal administration of BCG uniformly results in severe ulceration and eschar formation at the injection sites leading to secondary microbial invasion and regional lymphadenopathy. We now report the use of isoniazid (Nydrazid) as part of an active specific immunization regimen. Incorporation of isoniazid into the immunization procedure for 2 wk alleviates or reduces the side effects of BCG infection. Moreover, with proper consideration of BCG dosage, isoniazid does not impair the efficacy of the BCG plus tumor cell vaccines. (Author abstract) (31 Refs)

19. CHEMOIMMUNOTHERAPY FOR AUTOCHTHONOUS ACUTE RAT LEUKEMIAS.

Zeller WJ, Reusch K, Schmahl D
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany
Cancer Treat Rep; 66(2):391-394 1982

Eighty autochthonous acute rat leukemias that had been induced by ethylnitrosourea were used to compare the effect of single-drug therapy with vincristine, doxorubicin, or cytarabine with the effect of combination therapy using these three drugs with or without BCG-Pasteur F. The combination chemotherapy was clearly superior to the single-drug therapy. The best results (survival time; duration of remission) were achieved by vincristine, doxorubicin, and cytarabine plus BCG, although compared to the combinations without BCG, these results were not significant. (Author abstract) (9 Refs)

20. POSSIBLE ROLE OF MACROPHAGE-LIKE SUPPRESSOR CELLS IN THE ANTI-TUMOUR ACTIVITY OF BCG.

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Br J Cancer; 44(6):828-837 1981

The iv injection of high doses (3 mg) of BCG into C3H mice bearing a transplantable 3-methylcholanthrene-induced fibrosarcoma caused the regression of a significant proportion. This effect was most evident when the BCG was injected on the day of the graft, or 7 days later. The injection of this agent either 14 days before the graft, or in low doses (0.1 or 0.5 mg), or directly into the tumor (it) only prolonged the survival of the animals. Spleen cells from systemic high-dose BCG-treated mice were found to exert a strong nonspecific cytostatic effect in vitro that was not an artefact of the test conditions, and was not expressed by cells from low-dose animals. The cytostatic effect was shown to be caused by cells with the characteristics of macrophages, ie they were strongly adherent, unaffected by treatment with anti-Thy 1.2+C', radioresistant but heat-sensitive, and were detected in BCG-treated 'B' mice. The spleens of high-dose BCG-treated mice also contained suppressor cells that were capable of inhibiting the in vitro reactivity of normal T cells to PHA. Like the cytostatic effect, this suppressor activity was not detected in low-dose mice, and the cells responsible had the properties of macrophages; the effect was lost after the removal of adherent cells by sequential exposure to plastic and colloidal iron, but was conserved after treatment with anti-Thy 1.2+C'. T-cell-deprived animals, such as 'B' or nude mice, also developed suppressor-cell activity when treated with systemic high-dose BCG. Close parallels became evident between the in vivo anti-tumor activity of BCG, the in vitro cytostatic effect, and the suppressor-cell activity. We here discuss the possible role of suppressor cells in the mechanism of action of this agent. (Author abstract) (38 Refs)

21. TUMOR BEARER T CELLS SUPPRESS BCG-POTENTIATED ANTITUMOR RESPONSES. I. REQUIREMENTS FOR THEIR EFFECT.

Hawrylko E
Cellular Immunobiology Section, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cell Immunol; 66(1):121-138 1982

Mice bearing established syngeneic tumors fail to reject them when immunized according to protocols based on optimal conditions for BCG potentiation of specific delayed-type hypersensitivity (DTH) and antitumor immunity. Serum factors from mice bearing either the poorly immunogenic mastocytoma, P815 (MA), or the more antigenic sarcoma, Meth A, have been shown to depress both DTH and antitumor immunity. This report demonstrates that lymphoid cells adoptively transferred from these tumor-bearing hosts also can suppress the efferent and afferent phases of DTH to tumor-specific antigens in both BCG-primed and unprimed syngeneic hosts. Suppressor cells (SC) were detected in spleen, thymus, and lymph nodes draining the tumor site, but not in distant superficial lymph nodes. Maximal suppressor activity appeared 6 days after tumor implantation and wanted by 18 days. Suppression of the afferent phase of both the BCG-primed and unprimed responses was antigen specific; suppression of the efferent phase of the BCG-primed response was also specific but SC could partially suppress the unprimed responses to sheep red blood cells (SRBC). Amputation of 6-day-old tumors resulted in the disappearance of splenic SC within 2 days but did not affect SC in draining lymph nodes. SC suppressed DTH in a dose-dependent manner but even the highest doses tested did not totally eliminate the response. Depression of the peak DTH reaction was not accompanied by significant abrogation of antitumor activity. If, however, SC were transferred during the ongoing antitumor response, immunity was partially suppressed. Efferent-phase SC were sensitive to treatment with anti-Thy 1 sera and complement but were unaffected by B-cell depletion. (Author abstract) (29 Refs)

22. TUMOR BEARER T CELLS SUPPRESS BCG-POTENTIATED ANTITUMOR RESPONSES. II. CHARACTERISTICS OF THE EFFERENT PHASE SUPPRESSOR.

Hawrylko E, Mele CA, Stutman O
Cellular Immunobiology Section, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cell Immunol; 66(1):139-151 1982

T cells (Ts) from BALB/c mice bearing 6-day-old syngeneic Meth A tumors can mediate suppression of the efferent limb of the delayed-type hypersensitivity (DTH) response elicited by immunization with irradiated Meth A cells as well as the augmented response obtained when the immunogen is in oculated into BCG-primed sites. Ts in the spleen are Lyt 1-23+ and bear I-J determinants. Their induction is thymus dependent. Hydrocortisone depletes the thymus of Ts but spares Ts in the spleen. Ts are metabolically active and dividing as evidenced by their sensitivity to low doses of cyclophosphamide (CY) (20 mg/kg body wt), a 15-hr pulse with vinblastine (Vbl), and irradiation with 600 rad or more. Ts adhere to Sephadex G-10 columns but are unaffected by treatment with carbonyl iron and magnetism. Their phenotype and mechanism of action appear to be comparable to those of Ts2 cells defined in models of DTH to simple haptens. (Author abstract) (36 Refs)

23. INFLUENCE ON THE CELL CYCLE PROGRESSION OF HELA CELLS BY C PARVUM ACTIVATED MACROPHAGES.

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J Reticuloendothel Soc; 31(1):85-98 1982

Dual parameter flow cytometry has been utilized to study the effect of C parvum activated mouse macrophages on HeLa cells. Identification of tumor cells in the presence of macrophages was facilitated by their distinct fluorescence with propidium iodide and fluorescein conjugated antiplacental alkaline phosphatase (PAP). The two parameters determined simultaneously provided an accurate quantitative assessment of HeLa cells. Dose response relationships between normal (NMphi) and C parvum (CpMphi) activated macrophages simultaneously assayed by tritiated thymidine (3HTdR) incorporation or direct assessment of the absolute number of tumor cells per well indicated that flow cytometry was a sensitive method of determining growth inhibition and cytotoxicity. Following incubation with CpMphi, the majority of HeLa cells appeared to survive in the G0G1 phase of the cell cycle, irregardless of whether or not both growth inhibition and cytoxicity had occurred. HeLa cells isolated in the G0G1 phase by unit gravity sedimentation were readily destroyed by CpMphi. Surviving tumor cells did not enter into S phase. The large increase in PAP on these cells indicated their viability in this growth arrested state. Target cells predominantly in late S and G2 phase were also sensitive to the cytolytic mechanism of CpMphi.

However, the surviving cells were apparently not growth inhibited until they had passed through mitosis and entered the G1-S interphase. Prelabeled HeLa cells separated into different proportions of the various cell cycle phases were equally sensitive to activated macrophages. The results indicate that while cytotoxicity appears to occur throughout the cell cycle, growth inhibition is more specific and is a result of a block at or near the G1-S interphase. (Author abstract) (18 Refs)

24. INABILITY OF TUMOUR CELLS TO ELICIT THE RESPIRATORY BURST IN CYTOTOXIC, ACTIVATED MACROPHAGES.

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Immunology; 45(3):577-585 1982

Activated macrophages from Corynebacterium parvum-treated mice are cytotoxic to non-antibody-coated tumor cells and have an augmented respiratory burst potential when compared to resident macrophages. We have investigated the possible involvement of the respiratory burst as an effector mechanism in this type of tumor killing. Scavengers of toxic metabolites of oxygen such as catalase, superoxide dismutase, 2,3-dihydroxybenzoate, ethanol, and cytochrome c did not inhibit macrophage cytotoxicity in this system. To investigate whether or not neoplastic cells stimulate the macrophage respiratory burst, we exposed activated macrophages to viable tumor cells and monitored macrophage superoxide anion production, chemiluminescence, and hexose monophosphate shunt activity. None of these indicators of the macrophage respiratory burst was stimulated by the tumor cells towards which the macrophages were cytotoxic. The data suggest that the respiratory burst is not utilized as an effector mechanism in the non-antibody-mediated macrophage tumor cytotoxicity reaction. (Author abstract) (25 Refs)

MICROBIAL FRACTIONS AND EXTRACTS

25. ENDOTOXIN (LPS) STIMULATES IN VITRO MIGRATION OF MACROPHAGES FROM LPS-RESISTANT MICE BUT NOT FROM LPS-SENSITIVE MICE.

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J Immunol; 128(2):608-613 1982

LPS induces strikingly different inflammatory responses in LPS-resistant and -susceptible mice. The present study was made to investigate the effects of LPS on the in vitro migration of macrophages and polymorphonuclear leukocytes from such animals. LPS, in the absence of serum, stimulated the chemokinetic migration of elicited macrophages from the LPS-resistant C3H/HeJ and C57BL10/ScCR mice, whereas migration of macrophages from the susceptible C3H/HeN and C57BL10/SN mice was either unaffected or slightly depressed by LPS. Doses of LPS as low as 50 ng/ml induced chemokinesis of C3H/HeJ macrophages. The strain differences between resistant and susceptible mice were observed with several different LPS preparations. In contrast, macrophage chemotaxis towards zymosan- or LPS-activated mouse serum was similar in resistant and susceptible strains. Deproteinized LPS and lipid A preparations also induced migration of C3H/HeJ macrophages, whereas treatment of LPS with polymyxin B abolished its stimulatory effects. Macrophages from C3H/HeJ mice must therefore respond to the lipid A moiety of LPS. We found no evidence that the strain characteristic migratory responses to LPS were influenced by differential stimulation of arachidonic acid metabolism by LPS in the cells: indomethacin, an inhibitor of prostaglandin synthesis, did not alter migration to either LPS- or zymosan-activated mouse serum in macrophages from resistant or susceptible mice; in contrast, NDGA and ETYA, inhibitors of the production of potentially chemotactic HETE, reduced migration toward both LPS- and zymosan-activated mouse serum by C3H/HeJ macrophages and toward zymosan-activated mouse serum by C3H/HeN macrophages. Strain differences in migratory responses to LPS were restricted to macrophages in that polymorphonuclear leukocytes of both strains failed to respond to LPS. Interestingly, these in vitro findings correlate with some of the in vivo inflammatory responses to LPS in resistant and susceptible mice. (Author abstract) (31 Refs)

26. REDUCED ANTITUMOR AND IMMUNE-ADJUVANT ACTIVITIES OF THE SUB-CELLULAR FRACTIONS FROM GROUP A STREPTOCOCCUS.

Ryoyama K, Natsuume-Sakai S, Hirota H, Koshimura S
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Jpn J Exp Med; 51(6):335-344 1981

Antitumor and biological activities of subcellular fractions from Group A streptococcus (Su-strain) were investigated. In combined treatment with 5-fluorouracil (5-FU), both cell wall fraction (CWF) and protoplast membrane fraction (PMF) were slightly effective against Ehrlich carcinoma in outbred ddY mice, and were ineffective in the L1210 leukemia-B6D2F1 mouse system. Antitumor activity of OK-432 was abolished by disruption of the preparation. CWF inhibited growth of Yoshida sarcoma cells in culture in a dose-dependent manner, with PMF and cytoplasmic particle fraction (CPF) having less inhibitory activity. OK-432 and heated Su-cocci were both effective in increasing the median survival of BALB/c mice; the subcellular fractions were ineffective. Subcellular fractions did not effectively augment the antileukemic potential of B6D2F1 mice when mitomycin C-treated L1210 cells were simultaneously given with the fractions. Contact sensitivity responses were augmented in B6D2F1 mice treated with OK-432, heated Su-cocci, CWF or PMF prior to sensitization with picryl chloride; CPF and cytoplasmic soluble fraction were ineffective. Immunopotentiating activities of the subfractions were markedly diminished compared with those of OK-432 and heated Su-cocci. The reduced antitumor activities of the subcellular fractions may be due to their reduced immunopotentiating activities. (26 Refs)

CYTOKINE THERAPY

27. SCANNING ELECTRON MICROSCOPIC STUDY OF CHANGES IN THE SURFACES OF LYMPHOKINE-TREATED GUINEA PIG MACROPHAGES.

Onozaki K, Homma Y, Miura K, Hashimoto T

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J Reticuloendothel Soc; 30(6):471-481 1981

The surface architecture of guinea pig peritoneal exudate macrophages treated with partially purified lymphokines and cultured for different time periods was examined by scanning electron microscopy. Lymphokine-treated macrophages exhibited remarkable cell surface changes including enlarged petal-like ruffles as early as 2 hr after treatment. The characteristic ruffles were found in both rounded and spreading macrophages, indicating that the changes were common structural alterations of lymphokine-stimulated macrophages. However, macrophages in the control preparation or in the medium alone formed a few such enlarged ruffles. The formation of the unusual ruffles continued for 24 hr but disappeared after about 48 hr. Subsequently, the macrophages had numerous contracted cell surface ruffles with apparently smooth faces, and, after 72 hr, their surface architecture further changed to form more rough ruffles with acute angles. Because both macrophage migration inhibitory factor and macrophage activation factor were contained in the lymphokine preparation, the formation of such petal-like ruffles appeared to be related to the phenomena of migration inhibition and activation of macrophages. (Author abstract) (24 Refs)

28. HELPER FACTOR PRODUCTION IN MURINE SECONDARY SYNGENEIC MIXED LEUKOCYTE REACTIONS.

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J Immunol; 128(2):817-822 1982

Culture supernatants of murine thymocytes or spleen cells responding in a secondary syngeneic mixed leukocyte reaction (SMLR) were studied for their biologic effects on cell-mediated immune responses in vitro. Such supernatants contained helper factor(s) that facilitated the development of alloantigen-specific cytotoxic T lymphocyte (CTL) responses from thymocyte precursors. Thymocytes, but not spleen cells, required activation by allogeneic effect factor (AEF) in primary culture in order to proliferate and produce biologically active mediator(s) during a secondary SMLR. The same culture supernatants possessed, in some instances, weak T cell growth factor (TCGF; IL 2) activity. However, TCGF activity could be dissociated from helper factor(s) active in the CTL induction assay because some culture supernatants that had potent helper activity were devoid of TCGF activity. This lack of TCGF activity was not due to a lower degree of sensitivity of the TCGF assay or to the presence of a selective TCGF inhibitor in the SMLR-derived supernatants, indicating that the helper factor(s) studied is distinct from TCGF. Production of immunoregulatory lymphokines during the SMLR may serve as a physiologically relevant model for studying the role of T cell-derived lymphokines in immunoregulation. (Author abstract) (41 Refs)

29. FEEDBACK REGULATION OF IMMUNE RESPONSES BY IMMUNE COMPLEXES; POSSIBLE INVOLVEMENT OF A SUPPRESSIVE LYMPHOKINE BY FCRGAMMA-BEARING B CELL.

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J Immunol; 128(2):882-887 1982

Inoculations of antigen-antibody complexes (immune complexes) with the intact Fc portion generates suppressor cells in vivo by binding to FcRgamma on B cells via Fc portions. The cell type responsible for the suppression appears to be B cells bearing FcRgamma. Neither T cells nor macrophages participate in both the inductive and effective phases of this type of regulation. The suppression caused by splenic B cells, previously stimulated with immune complexes in vivo, is mediated by humoral factor(s) released from them. The suppressive factor(s) have H-2 gene product(s) coded by the right-hand side of the H-2 gene complex, but not for FcRgamma themselves or immunoglobulins. It has shared component(s) with suppressive B cell factor (SBF) released from FcRgamma+ B cells stimulated with immune complexes in vitro, and it resembles SBF in its mode of action. These findings indicate that immune complexes, the final products of antibody responses, control the immune responses by stimulating surface FcRgamma on B cells. It is of interest that this type of regulation functions in vivo. (Author abstract) (45 Refs)

30. APPEARANCE OF THREE LYMPHOKINES IN CULTURE SUPERNATANTS HARVESTED AT DIFFERENT TIMES.

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Dept. Microbiology, Univ. Queensland, St. Lucia, Qld. 4067, Australia

Immunol Lett; 4(1):21-26 1982

Factors responsible for WBC adherence inhibition (LAI), macrophage/WBC migration inhibition and acute erythrocyte-rosette augmentation (E-RA) were determined in culture supernatants of a fibrosarcoma induced in inbred CBA mice with 3-methylcholanthrene. Peritoneal cells from the mice were stimulated with the corresponding antigen and supernatants were prepared after incubation times of 1.0, 3.5, and 24 hr. Supernatants were tested by the indirect (two-stage) method on the same pool of indicator cells. The LAI inhibition factor was detected in both experiments in the 1 hr supernatant, in 1/2 at 3.5 hr, and not at all after 24 hr. The E-RA augmentation factor was found only in the 3.5 hr supernatant and the migration inhibition factor only in the 24 hr supernatant. Results indicate that the mediators responsible for the three in vitro reactions are different substances with different kinetics of production by stimulated cells. To assume only a single factor would involve consideration of a complex system of distinct inhibitors. (25 Refs)

31. PURIFICATION OF A LYMPHOID CELL LINE PRODUCT WITH LEUKOCYTE INHIBITORY FACTOR ACTIVITY.

Meshulam DH, Blair HE, Wong BL, Charm S, Minowada J, Rocklin RE

Enzyme Center, Tufts Univ. Sch. Medicine, Boston, MA, 02111

Proc Natl Acad Sci USA; 79(2):601-605 1982

Leukocyte inhibitory factor (LIF), a lymphokine that inhibits the random and directed migration of polymorphonuclear (PMN) leukocytes, was purified from a human non-T, non-B leukemia cell line (Reh). From 10 liters of serum-free supernatant, 1.3 ug of protein with LIF activity was obtained by the sequential use of affinity chromatography with concanavalin A-Sepharose, hydrophobic chromatography with hexylagarose, and gel filtration chromatography. The specific activity of LIF recovered represented an 80,000-fold purification over that of the initial crude serum-free supernatants, and the preparation at that point was estimated to be 80-90% pure. To both assess the purity of the preparation and provide a further purification step, Reh LIF activity recovered by the above procedures was subjected to isoelectric focusing. One major stainable protein band was identified; its isoelectric point was pH 5.4-5.5. Gels run in parallel for recovery of biologic activity revealed only one region (pH 5.4-5.5) with ability to inhibit PMN leukocyte migration. Iodination of Reh LIF resulted in a loss of biologic activity, but isoelectric focusing of this material revealed one major 125I-labeled band (pH 5.1) and several minor bands. The coincidence of biologic LIF activity with one stainable protein band as identified by isoelectric focusing implies that the final product may be homogeneous. (Author abstract) (21 Refs)

32. T CELL-SPECIFIC SUPPRESSOR FACTOR(S) WITH REGULATORY INFLUENCE ON INTERLEUKIN 2 PRODUCTION AND FUNCTION.

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J Immunol; 128(2):784-790 1982

In this study we report that alloantigen-activated spleen cells produce both amplifying and suppressive factors under the same conditions. Both types of soluble mediators, as detected in different assay systems, were present in the supernatants of in vivo sensitized and in vitro restimulated spleen cell populations and were separable by gel filtration. As shown by others, the amplifying factor (IL 2) was eluted in the size range of 30,000 mol wt. The suppressive factor(s) (SF) was eluted in the size range of 10,000 mol wt. SF was shown to inhibit the proliferative response of T cells to alloantigen, as well as the generation of regulatory T cells and cytotoxic T cells from their precursors when added at the beginning of the in vitro culture. Furthermore, SF inhibited the release of IL 2 from producer T cells but had no detectable effect on the interaction of IL 2 with receptive T cells. In addition it was shown that SF does not affect the generation of PFC from their precursors after activation by T cell-independent antigens. The results indicate that SF selectively acts on T cells and that it is involved in the regulation of the immune response by modulating early events in T cell activation. (Author abstract) (57 Refs)

33. T LYMPHOCYTES OF YOUNG AND AGED RATS. II. FUNCTIONAL DEFECTS AND THE ROLE OF INTERLEUKIN-2.

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J Immunol; 128(2):644-650 1982

Splenic T lymphocytes of aged Lewis rats respond to Con A and PHA with diminished 3H-TdR uptake compared with splenic T lymphocytes of young Lewis rats. After immunization with allogeneic tumor cells, uptake of 3H-TdR in mixed lymphocyte-tumor cultures and T cell cytotoxicity against tumor target cells are significantly lower with spleen cells of aged rats compared with those of young rats. The culture of spleen cells of aged rats with Con A results in a diminished conversion of Ia-positive T cells from Ia-negative precursors compared with similar cultures of spleen cells of young rats. Spleen cells of both young and aged rats produce high amounts of IL-2 in response to Con A stimulation. 'Old' T cells, however, bind relatively little IL-2, do not utilize it in culture, and do not response to exogenous IL-2 with enhanced 3H-TdR uptake as do 'young' T cells. In allogeneic MLTC, 'old' T lymphocytes produce little IL-2 compared with 'young' cells, and both 'young' and 'old' cells respond to exogenous IL-2 with enhanced 3H-TdR uptake and increased cytotoxic activity. The data suggest defects in the synthesis and/or recognition of IL-2 as well as defects in the regulation of Ia antigen expression may be responsible, in part, for the reduced T cell function in aged animals. (Author abstract) (45 Refs)

34. PRELIMINARY CHEMICAL AND BIOLOGIC CHARACTERIZATION OF (FC)TRF: AN FC FRAGMENT-INDUCED T CELL-REPLACING FACTOR.

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J Immunol; 128(2):590-594 1982

Fc fragment stimulation of Lyt-1+2-T lymphocytes triggers release of a T cell-replacing factor, here called (Fc)TRF. Chemical and biologic characterization of (Fc)TRF has been undertaken to provide information for its comparison with other T cell factors. Preliminary chemical characterization by column chromatography and isoelectric focusing suggest (Fc)TRF activity resides in a class of acidic molecules that fall into two size classes of 58-60,000 daltons and 35-40,000 daltons. This factor is distinct from interleukin 2 (IL 2) as it has no T cell growth-promoting or costimulator activity, although it can also be generated by Con A activation of murine spleen cells. By these results (Fc)TRF has been defined as a unique T cell-replacing activity that promotes differentiation of B lymphocytes to antibody-secreting cells. (Author abstract) (25 Refs)

35. CYTOKINE-DEPENDENT THYMOCYTE RESPONSES: CHARACTERIZATION OF IL 1 AND IL 2 TARGET SUBPOPULATIONS AND MECHANISM OF ACTION.

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J Immunol; 128(2):797-801 1982

The responsiveness of murine thymocytes to T cell mitogens was examined in the presence of highly purified preparations of IL 1 and IL 2. Fractionation of thymocytes by selective agglutination with peanut lectin (Arachius hypogeae) resulted in separation of two cell populations, each of which mediated distinctive responses to cytokine stimulation. The majority of thymus cells, agglutinated by the lectin (PNA+), were found to be unresponsive to mitogen in the presence of the macrophage-derived factor, IL 1; but showed marked proliferation when stimulated by mitogen in concert with the T cell-derived factor, IL 2. The nonagglutinated fraction, (PNA- cells) demonstrated substantial levels of proliferation after stimulation with mitogen in the absence of any exogenous factors. Moreover, IL 1 alone was highly mitogenic for PNA-thymocytes. This stimulation was further shown to result in the subsequent release of IL 2, as assessed by both the detection of IL 2 by lymphokine-dependent T cell lines and the inhibition of IL 1-dependent mitogenesis by the presence of anti-IL 2 monoclonal antibody. These results further substantiate the important immunoregulatory nature of these proteins and elucidates the possible role of these substances in the ontogeny of T cell responsiveness. (Author abstract) (33 Refs)

36. ANTIGEN-NONSPECIFIC HELPER FACTORS IN THE ANTIBODY RESPONSE.

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Fed Proc; 41(2):263-268 1982

Four biochemically distinct antigen-nonspecific factors have been shown to augment the antibody response to particulate thymic-dependent antigens, ie, heterologous erythrocytes. These factors are the lymphokines colony-stimulating factor, T cell-replacing factor, and interleukin 2, as well as the monocyte product interleukin 1. The immunoenhancing role of each of these factors in the antibody response is reviewed. A description of the biochemical properties of each factor, the biochemical separation of each factor for other helper factors, the separation of certain factors using different producing cells, and a description of the culture systems used to demonstrate helper activity are included. Questions concerning the target cell specificity and hence the mechanism of action of each factor are raised. Finally, recent data from several laboratories demonstrating the synergistic interactions of the helper factors in enhancing antibody synthesis are reviewed and models of B cell activation are presented. (Author abstract) (58 Refs)

37. THE EFFECTS OF LIPOPOLYSACCHARIDE, BCG-IMMUNE T LYMPHOCYTES, AND LYMPHOKINES ON GENERATION OF TUMORICIDAL PULMONARY MACROPHAGES IN SYRIAN HAMSTER.

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Exp Lung Res; 3(1):81-90 1982

The mechanism by which resident pulmonary macrophages from hamsters acquire cytocidal capacity was investigated. Adult male Syrian hamsters received 1.2 x 10(6) colony-forming units BCG by intratracheal instillation and were killed 6 wk later, or received two intratracheal instillations 6 wk apart and were killed 5 days after the second instillation. Macrophages and T cells were obtained from the pulmonary exudate. The tumoricidal capacity of pulmonary cells from BCG-immune animals was markedly enhanced in the presence of 50 ug/ml Escherichia coli lipopolysaccharide (LPS). Increasing concentrations of LPS resulted in corresponding increases in tumoricidal activity by the lavaged cells from BCG-immune and from BCG immune-rechallenged animals and by purified adherent cells from BCG immune-rechallenged hamsters. After 3 hr of coculture with BCG-immune T cells, pulmonary macrophages from untreated hamsters possessed tumoricidal capacity identical to those in continuous presence of immune T cells. Tumoricidal capacity of macrophages increased from 12-30% with the addition of 10% concanavalin A (Con A) supernatant fluid, and from 19%-31% in the presence of LPS plus Con A. Macrophages from untreated hamsters could not be activated for tumor cytotoxicity by in vitro treatment with LPS. Hamster pulmonary macrophages become responsive to LPS only after induction of an inflammatory exudate by rechallenge with BCG. (20 Refs)

38. MACROPHAGE ACTIVATION BY TUFTSIN AND MURAMYL-DIPEPTIDE.

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Mol Cell Biochem; 41:113-118 1981

Peritoneal macrophages from tuftsin or MDP-treated mice were tested for their cytostatic activity for tumor cell proliferation. Both substances are able to activate macrophages either after intravenous injection or after incubation in vitro with normal macrophages. But a stimulation as well as an inhibition of tumor cell growth can result from macrophage activation depending on the timing and dose injected. Restoration of the impaired cytostatic capacity of macrophages of mice observed with aging, is obtained by repeated administration of tuftsin. Normal and BCG-stimulated macrophages were examined for their regulatory activity on the proliferation of P815 tumor cells. Low density of macrophages per well determines a stimulation of target cell growth whether the macrophages are normal or activated. When the number of macrophages is increased, under conditions in which normal macrophages are not inhibitory. BCG- stimulated macrophages exert already a strong cytostatic activity. At high macrophage content it appears that normal macrophages can also display an inhibitory activity. Macrophage-tumor cell interactions are highly dependent on the concentrations and the state of activation of macrophages. (Author abstract) (20 Refs)

ADOPTIVE IMMUNIZATION AND RELATED APPROACHES

39. TUMOR-SPECIFIC IMMUNITY INDUCED BY SOMATIC HYBRIDS. III. PERSISTENCE OF ADOPTIVELY TRANSFERRED IMMUNITY SPECIFIC FOR TEPC-15 PLASMACYTOMA IN NORMAL BALB/C MICE.

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Dept. Microbiology-Immunology, Cancer Center, Medical and Dental Sch., Northwestern Univ., Chicago, IL, 60611

Cell Immunol; 65(2):373-379 1981

Immunity against TEPC-15 tumor cells was induced in BALB/c mice by injecting semi-allogeneic hybrid cells derived from fusion of TEPC-15 tumor cells with LM(TK(-)) cells of the C3H origin. Adoptive transfer of spleen cells from the immune mice into normal BALB/c recipients rendered them free from tumors following tumor challenge; the recipients were most significantly protected from the tumor when tumor cells were injected 7-14 days after the adoptive transfer of immune cells. Such immunity following adoptive transfer appeared to persist in the recipients for at least 60 days. Moreover, the tumor-specific immunity was consecutively transferable (more than 9 passages) into normal BALB/c recipients by serially passing spleen cells from the recipients every 14 days without further stimulation with the hybrid cells or inactivated TEPC-15 tumor cells. Such consecutive transfer of the immune spleen cells induced splenomegaly in the recipients: a two- to five-fold increase over normal spleen cell recipients. The ability of spleen cells to transfer immunity, but not splenomegaly, was abrogated by treatment with mitomycin C. These results suggest that proliferation of donor cells is necessary to transfer immunity, and that splenomegaly alone does not manifest such immunity in the recipients. (Author abstract) (23 Refs)

40. INDUCTION OF SPECIFIC CELL-MEDIATED CYTOTOXICITY IN VITRO BY MEANS OF RNA ISOLATED FROM ALLOGRAFTED MICE.

Holan V, Lipoldova M, Zadrazil S, Hasek M
Inst. Molecular Genetics, Czechoslovak Acad. Sciences, 163 37 Praha, Czechoslovakia
Folia Biol (Praha); 27(6):422-426 1981

Immune RNA was prepared by sensitization of B10.A mice with allogeneic skin grafts from C57BL/10Sn mice and extraction from spleens and lymph nodes in cold phenol-chloroform-isoamyl alcohol. The RNA extracts induced specific cell-mediated immunity in vitro in lymphocytes of normal B10.A mice, demonstrated by 3H-thymidine microcytoxicity assay in surviving cells of MC11 sarcoma induced in B10 mice or in cells of two Rous sarcoma virus-induced tumors in Wistar rats or DBA mice. The RNA immunospecific cytotoxi city persisted after deoxyribonuclease and pronase treatment but not after ribonuclease treatment, indicating that RNA activity is involved in the induction process. (16 Refs)

SEROTHERAPY AND RELATED APPROACHES

41. SELECTIVE KILLING OF LEUKAEMIA CELLS BY ANTIBODY-TOXIN CONJUGATES: IMPLICATIONS FOR AUTOLOGOUS BONE MARROW TRANSPLANTATION.

Krolick KA, Uhr JW, Vitetta ES
Dept. Microbiology, Univ. Texas Southwestern Medical Sch., Dallas, TX, 75235
Nature; 295(5850):604-605 1982

The recent development of tumor-reactive monoclonal antibodies has stimulated interest in their use in targeting toxic agents to tumor cells. One such approach involves the covalent coupling of tumor-reactive antibodies to the toxic peptide of the plant toxin, ricin. Such conjugates are highly effective in killing various tumor cells in vitro. Here we have used the murine B-cell tumor, BCL, in an adoptive transfer system capable of detecting 1-10 tumor cells, to demonstrate the effectiveness and specificity of an anti-immunoglobulin(Ig)-ricin A chain conjugate in deleting tumor cells from infiltrated murine bone marrow. We report that the transferred cells were able to repopulate the hematopoietic system of lethally irradiated mice and that in most mice the tumor did not recur. We discuss the implications of this approach for autologous bone marrow transplantation following supralethal tumor therapy. (Author abstract) (13 Refs)

42. BONE MARROW TRANSPLANTATION ACROSS MAJOR HISTOCOMPATIBILITY BARRIERS IN MICE. III. TREATMENT OF DONOR GRAFTS WITH MONOCLONAL ANTIBODIES DIRECTED AGAINST LYT DETERMINANTS.

Vallera DA, Soderling CC, Kersey JH
Dept. Therapeutic Radiology, Box 367, Mayo Memorial Building, 420 Delaware St., Southeast, Minneapolis, MN, 55455
J Immunol; 128(2):871-875 1982

We studied the effect of eliminating T cells from donor grafts of mice in a system in which bone marrow was transplanted across major histocompatibility barriers. BALB/c bone marrow (added as a source of hematopoietic stem cells) combined with equal volumes of spleen cells (added as a source of GVHD-promoting cells) was pretreated in vitro with monoclonal anti-Lyt-1.2 or Lyt-2.2 plus absorbed rabbit complement before injection into C57BL/6 total-body-irradiated recipients. Functional activity of anti-Lyt monoclonal antibodies was determined in CML assay. Treatment with anti Lyt-1.2 plus C did not have any anti-stem cell activity, as measured by CFU-S assay, and protected recipients from the onset of lethal GVHD. Treatment with Lyt-2.2 plus C also did not reduce CFU-S; however, mice receiving treated marrow did develop GVHD and were all dead by 2 mo, as were untreated control mice. Surviving 'anti-Lyt-1.2 + C chimeras' demonstrated a high percentage of donor mononuclear cells in their peripheral blood. Similar results were obtained when C3H/HeN donor BMS was treated with monoclonal anti-Lyt-1.1 plus C and injected into C57BL/6 recipients. These findings show that monoclonal antibodies directed against determinants unrelated to Thy-1 can eliminate T cells in the presence of C and successfully protect transplanted mice from lethal GVHD. They also suggest that these anti-Lyt antibodies may be useful tools in determining subpopulations of T cells that contribute to the development of GVHD. (Author abstract) (24 Refs)

43. ELIMINATION OF T-LYMPHOCYTES FROM HUMAN BONE MARROW WITH MONOCLONAL T-ANTIBODIES AND CYTOLYTIC COMPLEMENT.

Granger S, Janossy G, Francis G, Blacklock H, Poulter LW, Hoffbrand AB
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Br J Haematol; 50(2):367-374 1982

Complement-mediated cytolysis has been used to remove T-lymphocytes from suspensions of human peripheral blood and bone marrow. Selective T-cell removal was investigated by three monoclonal antibodies, OKT3, MBG6 and OKT11A. All three removed greater than 90% of T-cells but combinations were necessary to kill greater than 99% of T-cells in vitro. The macrophage-granulocyte and erythroid colony forming cells of the bone marrow were spared. The method can be applied on bulk BM samples during clinical BM transplantation and will be useful to establish whether the virtually complete removal of T-lymphocytes totally prevents transplant associated graft-vs-host disease in man. (Author abstract) (21 Refs)

44. MONOCLONAL ANTIBODIES THAT DETECT DIFFERENTIATION SURFACE ANTIGENS ON HUMAN MYELOMONOCYTIC CELLS.

Perussia B, Trinchieri G, Lebman D, Jankiewicz J, Lange B, Rovera G
Wistar Inst., 36th St. at Spruce, Philadelphia, PA, 19104
Blood; 59(2):382-392 1982

We describe here the production and characterization of several new monoclonal antibodies that recognize differentiation antigens present on human cells of the myelomonocytic lineage. The lineage and the stage specificities of our reagents (myeloid-, monocytic-, and myelomonocytic-specific) were determined on the basis of their reactivity with human cell lines and with human peripheral blood and bone marrow cells. Cross-competition experiments demonstrated that some of the antibodies react with the same or closely associated antigenic determinants. Five antigens have been identified in this way: one present on myeloid, one on monocytic, and three on both myeloid and monocytic cells. The possible relationship of our antibodies with other established monoclonal antibodies is discussed, in addition to their use in the in vitro study of the differentiation pathways of human hemopoietic cells and in the characterization of leukemias. (Author abstract) (29 Refs)

45. A COMPARATIVE STUDY OF THE USE OF MONOCLONAL ANTIBODIES USING THREE DIFFERENT IM MUNOHISTOCHEMICAL METHODS: AN EVALUATION OF MONOCLONAL AND POLYCLONAL ANTIBODIES AGAINST HUMAN PROSTATIC ACID PHOSPHATASE.

Naritoku WY, Taylor CR
Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
J Histochem Cytochem; 30(3):253-260 1982

The use of immunohistochemical methods has been advocated for the detection and localization of prostatic acid phosphatase in paraffin sections of human prostate. This article explores the possible advantages of utilizing monoclonal antibodies in this method. Monoclonal antibodies, specific for human prostatic acid phosphatase, were integrated into three different immunohistochemical procedures. In the first method, a three-layer peroxidase-antiperoxidase (PAP) system was employed; the monoclonal antibody was followed by rabbit bridge antibody directed against mouse immunoglobulin and mouse PAP complex. The second method was a three-layer system utilizing biotin-labeled horse anti-mouse antibody as 'bridge' antiserum between the primary monoclonal antibody and an avidin-biotin-horseradish peroxidase complex. The third method was a four-layer system; the monoclonal antibody was followed by rabbit anti-mouse serum, swine anti-rabbit immunoglobulin as the bridge antibody and rabbit PAP complex. It was found that some, but not all, monoclonal antibodies can be used for the detection of prostatic acid phosphatase in paraffin sections. The four-layer PAP method was found to be the most sensitive method of the three systems tested; however, the avidin-biotin method required the least amount of time. No significant difference in the quality of staining was observed between monoclonal antibodies and carefully absorbed conventional antiserum. (Author abstract) (12 Refs)

46. EFFECT OF ESTRADIOL AND DEGREE OF CELL DIFFERENTIATION ON HUMAN MELANOMA SUSCEPTIBILITY TO KILLING BY MONOCLONAL ANTIBODIES.

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Immunol Lett; 4(1):59-64 1982

The relationship of antigenic determinants of melanotic and amelanotic human malignant melanoma cells to responsiveness to estradiol (ES) was studied. Cultures grown in the absence and presence of ES were used to develop various cell lines: a non-responsive melanotic (E-M+ShA) was derived from ES-responsive melanotic (E+M+ShA) and an ES-responsive amelanotic (E+M-SR) was derived from ES-non-responsive amelanotic (E-M-SR). Cellular responsiveness to hormone was determined by incubation with insulin, with addition of (3H)thymidine after 72 hr. Spleen lymphocytes from mice preimmunized with E+M+ShA, E-M+ShA, E-M-SR, and E+M-SR were fused with murine non-producer myeloma cells to obtain mouse-mouse hybridoma cultures synthesizing monoclonal antibodies against human malignant melanoma. Complement-dependent cytotoxic activity of the monoclonal antibodies varied from one hybridoma to another. Results indicate that the antigenic determinants of melanoma cells vary from one cell line to another; efficiency of complement-mediated killing is a function of responsiveness to estradiol and degree of melanogenesis. (37 Refs)

47. HUMAN PROSTATE SPECIFIC AND SHARED DIFFERENTIATION ANTIGENS DEFINED BY MONOCLONAL ANTIBODIES.

Frankel AE, Rouse RV, Herzenberg LA
Dept. Oncology, Stanford Univ., Palo Alto, CA, 94305
Proc Natl Acad Sci USA; 79(3):903-907 1982

Splenic lymphocytes of BALB/c mice immunized with membrane-enriched fractions of human benign prostatic hyperplasia tissues were fused with the NS-1 light chain-secreting murine myeloma cell line. This generated hybridoma cultures that secreted immunoglobulins reactive in solid-phase radioimmunoassays with membrane preparations of prostatic tissues but not with membrane preparations of apparently normal human liver, spleen, thymus, or erythrocytes. After further screening of immunoglobulin reactivities and cloning of cultures, eight monoclonal antibodies were chosen that demonstrated reactivity with human prostate tissues. These monoclonal antibodies could be placed into at least three major groups - epithelium-specific, polyepithelial, and stroma-specific - on the basis of differential binding to the surfaces of various component cells in the prostate and other epithelia. Two antibodies defined unique protein antigens specific for prostate epithelia that were not crossreactive with prostatic acid phosphatase or the recently described 'prostatic antigen.' These antibodies also detected antigens on malignant prostate tissues as well as other malignant tissues. Four antibodies defined three unique polyepithelial protein antigens (two of the antibodies were different isotypes defining the same protein). Each of the polyepithelial antigens was expressed on a different spectrum of normal epithelial tissues. Two displayed brain tissue crossreactivity, one was present on pancreas, and one was present on platelets. The two antibodies that detected prostatic stromal protein antigens showed different spectra of reactivities. One antibody reacted with apparently all prostatic stromal cells as well as endothelial cells in the prostate and other organs. The other antibody apparently reacted with all prostatic stromal cells as well as myoepithelial and muscle cells in other organs. (Author abstract) (17 Refs)

48. IDENTIFICATION OF HUMAN ACINAR CELL CARCINOMA BY MONOCLONAL ANTIBODY AND IN VITRO DIFFERENTIATION.

Parsa I
Dept. Pathology, State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203
Cancer Lett; 15(2):115-121 1982

Identification of precursor cells of tumors induced by methylnitrosourea (MNU) in organ culture using monoclonal antibody to acinar cells is described. Nude mice were inoculated sc with carcinomas induced by MNU in organ-cultured human pancreas. Tumor nodules developed after 8 wk and were used to establish cell lines. Both monoclonal antibody to acinar cell surface marker produced by hybridoma and in vitro tumor cell differentiation were used to detect tumors of acinar cell origin. One of 14 tumors studied proved to be of acinar cell origin. Fluorescent microscopy revealed strong surface fluorescence. The intensity of fluorescence was much higher than that in normal acinar cells and varied considerably from cell to cell and also on each cell surface. The acinar origin of the tumor was confirmed by its differentiative features after 7 wk of culture. (12 Refs)

49. SELECTING BINDING AND COMPLEMENT-MEDIATED LYSIS OF HUMAN HEPATOMA CELLS (PLC/PRF/5) IN CULTURE BY MONOCLONAL ANTIBODIES TO HEPATITIS B SURFACE ANTIGEN.

Shouval D, Wands JR, Zurawski VR, Isselbacher KJ, Shafritz DA
(c/o Shafritz) Dept. Medicine and Cell Biology, Liver Res. Center, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Proc Natl Acad Sci USA; 79(2):650-654 1982

High-affinity 125I-labeled monoclonal antibodies to hepatitis B virus surface antigen (HBsAg) bind to a human hepatocellular carcinoma cell line, PLC/PRF/5, which synthesizes and secretes HBsAg. These monoclonal antibodies of the IgG1, IgG2a, and IgM isotypes are directed against different antigenic determinants on HBsAg and, in the presence of complement, both anti-HBs IgG2a and IgM, but not anti-HBs IgG1, lyse PLC/PFR/5 cells in culture. Although there is a low level of anti-HBs binding (especially with anti-HBs IgM) to human hepatoma cell lines which do not synthesize HBsAg (SK-Hep 1 and Mahlavu cells), this interaction does not lead to complement-mediated cell lysis and is thought to be nonspecific. Minimal binding of 125I-labeled anti-influenza HA antigen IgM binding to PLC/PRF/5 cells was also detected, but this likewise did not lead to complement-mediated cell lysis. These results indicate that a human hepatocellular carcinoma cell line, persistently infected with hepatitis B virus, can be recognized and lysed by monoclonal antibodies directed against specific determinants of HBsAg. Monoclonal antibodies to this viral envelope protein may prove to be useful immunodiagnostic and immunotherapeutic agents when such viral epitopes are expressed on the surface of infected cells. (Author abstract) (33 Refs)

50. MONOCLONAL ANTIBODIES TO TWO MOUSE BLADDER CARCINOMA ANTIGENS.

Hellstrom I, Rollins N, Settle S, Chapman P, Chapman WH, Hellstrom KE
Program Tumor Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Int J Cancer; 29(2):175-180 1982

Carcinomas of the urinary bladder of mice were induced by 3-methyl-cholanthrene or FANFT [(4-5-nitro-2-furyl)-2-thioazolyl formamide]. On transplantation in vivo, tumor lines consisting of well-differentiated transitional-cell carcinomas were established. Some tumors were also explanted in vitro. A rat was immunized with a pool of carcinomas and normal bladder tissue and its spleen cells were hybridized with NS-1 mouse myeloma cells. Supernatants of hybrid cells ('hybridomas') were screened for antibody binding to antigens present in bladder carcinomas but not in normal syngeneic urinary bladder, with cell extracts as targets. Hybridomas that appeared to have the required specificity were cloned, tested further against transitional-cell bladder carcinomas, an anaplastic bladder tumor, rhabdomyosarcomas, a mammary carcinoma, myelomas and lymphomas, and normal adult urinary bladder, kidney, lung, spleen, heart, brain, thymus, and whole embryo. Antibody formed by one hybridoma, 2H5, gave significant binding to membranes from five of seven transitional-cell carcinomas but not to membranes from any other tissues. A second hybridoma, IE6, formed antibody to an antigen present in bladder carcinomas and normal liver and, in smaller amounts, in several other normal and neoplastic tissues. Fluorescence microscopy established that both antigens were present at the cell surface of transitional-cell bladder carcinomas. Immunoprecipitation and SDS-polyacrylamide gel electrophoresis were used to identify the target antigens from 125I-labeled cell membrane proteins. The antibody formed by 2H5 was found to identify a protein with a mol wt in the range of 140 kilodaltons, which was detected in transitional-cell bladder carcinoma and, in small amounts, in normal bladder. The molecular nature of the antigen defined by hybridoma IE6 is not known. (Author abstract) (25 Refs)

51. DEFINITION OF A THY-1 DETERMINANT ON HUMAN NEUROBLASTOMA, GLIOMA, SARCOMA, AND TERATOMA CELLS WITH A MONOCLONAL ANTIBODY.

Seeger RC, Danon YL, Rayner SA, Hoover F
Dept. Pediatrics, Center Health Sciences, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
J Immunol; 128(2):983-989 1982

Neuroblastoma, glioma, rhabdomyosarcoma, leiomyosarcoma, and teratoma cells were shown to express an antigenic determinant of human Thy-1 with monoclonal antibody 390 (ab 390). Specificity of ab 390 for a determinant on Thy-1 was shown in three ways. (1) The distribution of antigenic determinant 390 (ag 390) among normal cells and tissues was that of human Thy-1. Quantitative absorption of ab 390 with adult tissues demonstrated a large quantity of ag 390 associated with brain, at least 90-fold less associated with kidney, and 150 to 10,000-fold less associated with lung, thymus, liver, adrenal, colon, and muscle. Ab 390 reacted strongly with cultured fibroblasts and also with 12% of thymocytes; it did not react with blood monocytes, lymphocytes, erythrocytes, or with bone marrow cells. (2) A molecule was isolated from deoxycholate solubilized human brain membranes by ab 390 affinity chromatography with Mr = 24,000. (3) Human brain Thy-1 that was purified by lentil lectin affinity chromatography specifically inhibited binding of ab 390 to LA-N-1 human neuroblastoma cells. In studies of 29 cultured tumor cell lines, ab 390 reacted strongly with gliomas and moderately with neuroblastomas, a rhabdomyosarcoma, a leiomyosarcoma, and teratomas. Its reactivity with medulloblastoma, melanoma, and carcinoma cell lines was weak or insignificant. A molecule with Mr = 26,000, which is the mw of fibroblast associated Thy-1, was purified from membranes of a neuroblastoma and a glioma cell line. Quantitative absorption of ab 390 with 50 noncultured tumors demonstrated that neuroblastomas, gliomas, and soft tissue sarcomas can express more ag 390 than all adult tissues except brain. Significant heterogeneity in the quantity of ag 390 associated with individual tumors within these positive classes was observed. These data suggest a variety of human tumor cells express Thy-1 on their surfaces. This expression appears to be appropriate for neuroblastoma, glioma, rhabdomyosarcoma, and leiomyosarcoma cells because normal cells of these same lineages also can express Thy-1. (Author abstract) (33 Refs)

52. B LYMPHOBLAST ANTIGEN (BB-1) EXPRESSED ON EPSTEIN-BARR VIRUS-ACTIVATED B CELL BLASTS, B LYMPHOBLASTOID CELL LINES, AND BURKITT'S LYMPHOMAS.

Yokochi T, Holly RD, Clark EA
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J Immunol; 128(2):823-827 1982

Two new cell surface antigens expressed on B lymphoblastoid cell lines (B-LCL) were defined with cytotoxic mouse monoclonal antibodies. One marker, BB-1 (for B lymphoblast antigen-1), was detected on human and nonhuman primate B-LCL, Epstein-Barr virus (EBV)-activated B cell blasts, most Burkitt's lymphomas, and Ia+ B lymphoblast-like myelomas.

Polyclonal B cell activators such as pokeweed mitogen (PWM) and lipopolysaccharide (LPS) also induced the expression of BB-1 on immunoglobulin (Ig)-positive cells.In contrast, BB-1 could not be detected on normal lymphoid tissues by complement-dependent cytotoxicity and immunofluorescence (IF) assays or by analysis with a fluorescence-activated cell sorter (FACS). T cell blasts, T cell leukemias, and pre-B cell or erythroblastic leukemia cell lines were also BB-1 negative. Of particular interest was the finding that BB-1 was expressed on the Jijoye lymphoma but only marginally on a subline of Jijoye, P3HR-1, that lacks receptors for EBV and produces a defective virus incapable of transforming lymphocytes. A second lymphoblast antigen (LB-1) unlike BB-1, was present on both T and B cell blasts and virus-transformed T- and B-LCL but not on normal lymphoid tissues. (Author abstract) (50 Refs)

53. DEVELOPMENT OF A MONOCLONAL ANTIBODY AGAINST A TUMOR-ASSOCIATED ANTIGEN.

Peng WW, Bressler JP, Tiffany-Castiglioni E, De Vellis J
Lab. Nuclear Medicine and Radiation Biology, Univ. California, Los Angeles, CA, 90024
Science; 215(4536):1102-1104 1982

A monoclonal antibody-producing hybrid cell line was obtained by fusing mouse myeloma cells with spleen cells from a mouse immunized with C6 glioma cells. This antibody binds to a specific cell-surface antigen that is present on C6 rat glioma cells, transformed astrocytes and oligodendrocytes, and a human glioma cell line but is absent on a normal glial cell line, fibroblasts, and primary cultures of astrocytes and oligodendrocytes. The antigen also appears on tumor tissue of transformed oligodendrocytes but not on normal brain tissue. (Author abstract) (18 Refs)

ANIMAL MODELS OF BIOLOGICAL THERAPY

54. IMMUNE RESPONSE OF BALB/C MICE TO PHTHALATE: CHARACTERIZATION OF A NEW AND USEFUL MODEL FOR STUDYING IMMUNE REGULATION.

Bankert RB, Mayers GL
Dept. Immunology Res., Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Immunol Commun; 10(6):457-481 1981

The humoral immune response to a unique haptenic determinant has been characterized at the single cell level. We report here that the hapten, phthalate, when conjugated to keyhole limpet hemocyanin (4-azophthalate-KLH) is highly immunogenic in adult BALB/c mice, and that the immunogenicity of the hapten is largely restricted to the two charged carboxylate groups on phthalate. Based upon plaque-forming cell (PFC) inhibition with increasing concentrations of free phthalate, relative affinity distribution profiles of antibody-forming cells have been established for individual mice. The antibody-forming cells in the spleens of these mice consist of five or six individual relative affinity sets. PFC inhibition studies with hybridomas secreting phthalate specific monoclonal antibodies reveal, as expected, a more restricted inhibition profile. The majority of PFC produced by the hybridomas could be assigned to one of the relative affinity sets. PFC inhibition studies employing a panel of cross-reactive phthalate analogs as inhibitors, have made it possible to segregate the splenic antibody-forming cell population further into distinct fine specificity sets. The recognized immunodominance of the two negatively charged carboxylate groups of phthalate and the rigid positioning of substituted charged groups on the phthalate analogs are unique to this hapten system and they are fundamental to the meaningful interpretation of the fine specificity data generated by the inhibition studies reported here. The ability to compartmentalize the phthalate response into relative affinity and fine specificity sets at the single cell level has made it possible for us to restrict our studies of immune regulation to a defined and manageable portion of a conventional thymic dependent B cell repertoire. (Author abstract) (24 Refs)

CLINICAL IMMUNOLOGY

55. PERSISTENCE OF ANTIBODY AFTER THE ADMINISTRATION OF INFLUENZA VACCINE TO CHILDREN WITH CANCER.

Sumaya CV, Williams TE
Dept. Pediatrics, Univ. Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX, 78284
Pediatrics; 69(2):226-229 1982

Children with cancer who received an intramuscular injection of inactivated split or whole bivalent (A/New Jersey/76-A/Victoria/75) influenza virus vaccine during the fall of 1976 were tested up to 18 mo later for the persistence of antibody. Titers of antibody greater than or equal to 10 to influenza A/New Jersey/76 virus were present in the sera of 34 children 2 wk after immunization. The geometric mean titer was 40.0. Eighteen mo later a titer greater than or equal to 10 was present in 13 (38%) children; the geometric mean titer was 8.5. Of 36 children with a titer of antibody greater than or equal to 10 to A/Victoria/75 virus 2 wk after immunization, 34 still had a detectable titer in the later examination. The geometric mean titer declined from 65.3 to 25.6. Titers of antibody to B/Hong Kong/72 virus (not included in the vaccine) remained relatively stable. In 11 children the usual chemotherapy was discontinued during the study. The shorter persistence of antibody to A/New Jersey/76 virus, in contrast to that of the other two influenza viruses tested, was associated with a lack of prior exposure to the virus and the absence of subsequent natural infection with this virus or an antigenically related subtype. The potential effect of cancer chemotherapy on the persistence of antibody levels is unclear. (Author abstract) (18 Refs)

56. IMMUNE COMPLEXES AND CIRCULATING ANTIBODIES AGAINST AUTOLOGOUS LEUKAEMIC CELLS IN PATIENTS WITH ACUTE LEUKAEMIAS.

Bertini M, Galetto G, Comoglio PM
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Immunology; 45(3):569-575 1982

Serum of patients with different forms of acute leukemias were analyzed either for the presence of circulating antibodies against autologous leukemic cells or for that of soluble immune complexes. At the moment of their diagnosis, 12/25 patients with different types of leukemias, showed circulating serum immunoglobulins capable of binding to the leukemic cell surface (LCS). These anti-LCS immunoglobulins were of the IgG class and were detectable by a binding assay employing glutaraldehyde-fixed target cells and radioiodinated Staphylococcus aureus Protein A. Their digestion with pepsin showed that the site involved in the binding was in the F(ab')2 fragment. The anti-LCS immunoglobulins were observed in patients with non-lymphatic leukemias but not in the four cases of acute lymphocytic leukemia studied. Forty percent of the patients with anti-LCS immunoglobulins had high levels of circulating immune complexes, detectable by a competitive test with bovine conglutinin and an enzymatically-active antigen-antibody probe. After cytostatic chemotherapy, the level of circulating immune complexes decreased in all the patients, while the anti-LCS immunoglobulins remained constantly detectable and appeared also in those who were negative at the day of the diagnosis. (Author abstract) (36 Refs)

57. HUMAN T-CELL MALIGNANCIES: CORRELATIVE CLINICAL, HISTOPATHOLOGIC, IMMUNOLOGIC, AND CYTOCHEMICAL ANALYSIS OF 23 CASES.

Knowles DM, Halper JP
Coll. Physicians and Surgeons, Lab. Surgical Pathology, Columbia Univ., 630 West 168th St., New York, NY, 10032
Am J Pathol; 106(2):187-203 1982

Twenty-three T-cell neoplasms were investigated for their reactivity with the OKT monoclonal antibodies and expression of certain cytochemical markers. Fourteen neoplasms with diverse histopathologic features, T-cell chronic lymphocytic leukemia, mycosis fungoides, the Sezary syndrome, T-immunoblastic sarcoma, and a pleomorphic large-cell lymphoma, expressed the T helper cell phenotype, OKT3+T4+. Nine other neoplasms displayed marked inter- and intra-tumor heterogeneity. Seven of these cases, lymphoblastic lymphoma, T-cell acute lymphoblastic leukemia, and tumors with features of T-immunoblastic sarcoma or the multilobated lymphoma of Pinkus, expressed intrathymic phenotypes. The other two cases, a lymphoblastic lymphoma and a so-called Lennert's lymphoma, expressed the previously undescribed OKT3+T10+ phenotype. These studies demonstrate that the T-cell malignancies are divisible into phenotypes corresponding to normal maturational stages of T-cell differentiation and functionally distinct T-cell subsets. Such studies should provide a basis for understanding the biologic heterogeneity, clinical diversity, and significance of the variable cytomorphologic characteristics of T-cell malignant tumors and assist in the further delineation of normal human T-cell heterogeneity. (Author abstract) (57 Refs)

58. IMMUNOLOGIC CLASSIFICATION OF LYMPHOCYTIC LEUKEMIAS BASED ON MONOCLONAL ANTIBODY-DEFINED CELL SURFACE ANTIGENS.

Schroff RW, Foon KA, Billing RJ, Fahey JL
Medical Immunology Res. Lab., Dept. Microbiology and Immunology, Univ. California, Los Angeles, CA, 90024
Blood; 59(2):207-215 1982

A panel of monoclonal antibodies reactive with normal lymphocyte subsets was used to classify cases of lymphocytic leukemia on the basis of cell surface antigen expression. The antibodies employed were commercially available and included a common framework HLA-DR antibody, two pan-T antibodies (Leu-1 and OKT-3), and antibodies defining cytotoxic/suppressor (Leu-2 and OKT-8) and helper/inducer (Leu-3 and OKT-4) subpopulations of normal T lymphocytes. Cases of ALL could be subgrouped into non-T non-B, pre-T and T-ALL on the basis of reactivity with HLA-DR, Leu-1, and OKT-3 antibodies. Leukemic cells from patients with T-cell CLL could be divided into Leu-2/OKT-8 reactive and Leu-3/OKT-4 reactive subpopulations, as well as a subgroup in which the majority of cells were unreactive with either of these antibodies. With the exception of one individual, all Sezary cell leukemias expressed a phenotypic pattern similar to that of the Leu-3 subgroup of T-CLL. Malignancies of B-cell lineage (B-CLL, prolymphocytic leukemia, and lymphosarcoma) that were examined were reactive with both the HLA-DR and Leu-1 antibodies. On the contrary, normal B lymphocytes and lymphoid cell lines of B-cell origin did not express surface antigens recognized by the Leu-1 antibody. (Author abstract) (56 Refs)

59. B CELL, HELPER T CELL, AND SUPPRESSOR T CELL ABNORMALITIES CONTRIBUTE TO DISORDERED IMMUNOGLOBULIN SYNTHESIS IN PATIENTS FOLLOWING BONE MARROW TRANSPLANTATION.

Korsmeyer SJ, Elfenbein GJ, Goldman CK, Marshall SL, Santos GW, Waldmann TA
Metabolism Branch, NCI, NIH, Bethesda, MD, 20205
Transplantation; 33(2):184-190 1982

The pathogenic mechanisms responsible for the hypogammaglobulinemia that occurs in patients who have undergone bone marrow transplantation were studied using peripheral blood lymphocytes in an in vitro immunoglobulin biosynthesis assay. None of the nine marrow recipients between 2 and 15 mo after transplantation produced normal amounts of IgG, IgA, or IgM in response to pokeweed mitogen (a T cell-dependent activator). However three of these same patients responded to Epstein-Barr virus (a helper T cell-independent activator), suggesting that these possessed responsive B cells. Cocultures of the marrow recipients' lymphocytes with lymphocytes from their respective donors or other normal subjects documented excessive suppressor cell activity in five cases. These suppressor cells frequently had profound activity (greater than 80% suppression of the immunoglobulin synthesis of cocultured normal cells), were predominantly radioresistant, and were T cells in the cases where analyzed. Helper T cell activity for immunoglobulin synthesis was not demonstrable in seven of the nine cases. In addition, four of the patients apparently possessed defective B cells. Although most patients had combined defects of several lymphocyte subpopulations, it appeared that either an isolated helper T cell or isolated B cell deficiency was sufficient to result in altered Ig synthesis. In this regard, two patients had demonstrable helper T cell defects with partially responsive B cells and no excessive suppressor activity. Interestingly, these two patients were experiencing a recurrence of their hypogammaglobulinemia following a period of normalized immunoglobulin levels. Thus, defects within all lymphocytic elements involved in the response and regulation of immunoglobulin synthesis were identified and may contribute to the humoral immunodeficiency which follows marrow transplantation. (Author abstract) (25 Refs)

60. IMMUNOLOGIC ASPECTS OF THE PROSTATE.

Lubaroff DM, Reynolds CW, Canfield L, McElligott D, Feldbush T
Dept. Urology, Univ. Iowa, Iowa City, IA, 52242
Prostate; 2(3):233-248 1981

Present knowledge of tumor immunology is reviewed, and recent research results using the Dunning R3327 tumor of the Copenhagen rat as an immunologic model of prostatic adenocarcinoma and continuing work, are described. The R3327 tumor, a well-differentiated adenocarcinoma which will grow into the sc space of the flank or within the prostate is described, and its histological appearance is shown. Earlier results included cryodestruction of the primary R3327 tumor by trocar probe procedure and demonstration of tumor-specific antigens and production of immune responses to them in xenogeneic, allogeneic, and syngeneic immunizations. Cell-mediated responses have been successfully demonstrated, including a nonspecific or natural killer activity in lymph nodes, spleen, and peripheral blood. Cryosurgery + BCG have been demonstrated to induce a tumor-protective immune response in the R3327 system. Problems associated with immunotherapy are reviewed, and studies demonstrating reduced immunocompetence in patients with prostatic cancer or benign prostatic disease compared to normal individuals are described. (26 Refs)

61. EFFECTS OF ACTIVATED T CELLS ON NATURAL KILLING.

Knight RA, Fitzharris P

I.C.F.R. Human Tumour Immunology Group, Univ. Coll. Hosp. Medical Sch., University St., London WC1E 6JJ, England

Immunology; 45(3):513-519 1982

Two populations of human blood lymphocytes, one forming rosettes with sheep erythrocytes, the other non-rosetting, are cytolytic in vitro for several long term cultured tumor-derived cell lines. A particular breast cancer-derived target cell (MDA 157) is only killed by the non-rosetting effector. Rosetting cells from normal donors infected or immunized with influenza virus augment cytolytic activity on MDA-157 targets by non-rosetting effector cells. Similar augmenting activity can be induced by incubating the rosetting population with sources of immune (gamma), but not leukocyte (alpha) interferon in vitro. This augmentation of cytolytic activity does not require compatibility at the major histocompatibility locus between the augmenting and effector populations. (Author abstract) (22 Refs)

62. IMMUNOCHEMICAL AND FUNCTIONAL ANALYSIS OF IA-LIKE ANTIGENS ON HUMAN MONOCYTE-MACROPHAGES WITH MONOCLONAL ANTIBODIES.

Ng AK, Zhang YH, Russo C, Ferrone S

Dept. Pathology, Columbia Univ., 630 W. 168th St., New York, NY, 10032

Cell Immunol; 66(1):78-87 1982

The distribution, structural profile, and functional properties of Ia-like antigens synthesized by human monocyte-macrophages have been analyzed using monoclonal antibodies to common determinants of these antigens. Up to 45 and 70%- of monocyte-macrophages isolated from the fluid of blisters induced with cantharidin and from peripheral blood, respectively, react with monoclonal antibodies to human Ia-like antigens. The level of Ia-like antigens on monocytes-macrophages appears to be similar to that on cultured B lymphoid cells. Monoclonal antibodies to common determinants of Ia-like antigens specifically block antigen presentation by monocyte-macrophages to T lymphocytes as well as proliferative response to T lymphocytes to autologous and allogeneic monocytes-macrophages. These results indicate that common determinants of Ia-like antigens play a role in the interaction of monocytes-macrophages with T lymphocytes. (Author abstract) (28 Refs)

REVIEWS

63. BIOLOGICAL RESPONSE MODIFIER THERAPY–AN OVERVIEW.

Oldham RK

Biological Response Modifiers Program, Div. Cancer Treatment, NCI, Frederick Cancer Res. Center, Frederick, MD

Cancer Bull; 33(6):244-250 1981

The Biological Response Modifiers Program (BRMP) is described. BRMP is a comprehensive program involved in clinical and laboratory research with extramural and intramural components, to investigate, develop, and bring to clinical trial potential therapeutic agents that may alter biological responses important in cancer growth and metastasis. Criteria for successful screening of biological response modifiers (BRM) and efficacy testing of promising BRM in preclinical studies are discussed. Clinical trials with BRM require a different approach than the traditional approach used to test new drugs. Whereas drugs are initially tested for toxicity and then for antitumor activity, BRM must also be tested for an ability to modify the appropriate biologic response. Although the BRMP continues to direct a considerable portion of funds toward interferon-related research, procurement, and clinical trials, a broader approach is being developed for the thymosins, retinoids, lymphokines, antisuppressor cell monoclonal antibody, and antitumor cell monoclonal antibody. Increased support for monoclonal antibody trials and lymphokine trials is anticipated. A major effort in the use of monoclonal antibody as a carrier for toxic compounds in an attempt to increase the specificity of cancer therapy is expected. Clinical testing of the use of lymphokines to manipulate the immune response and the use of cytokines in an attempt to control tumor growth and metastasis directly will be emphasized. (39 Refs)

64. CLINICAL INVESTIGATION OF THE INTERFERONS IN HUMAN CANCER.

Gutterman JU

Dept. Clinical Immunology and Biological Therapy, Univ. Texas M.D. Anderson Hosp . and Tumor Inst., Houston, TX

Cancer Bull; 33(6):271-278 1981

Properties making interferon a unique antitumor agent, clinical investigations in patients with solid tumors and hematologic neoplasms, and prospects for future interferon research including the study of pure biosynthetic interferons are reviewed. Recent studies have demonstrated that impure leukocyte interferon administered in relatively low doses can induce regression of metastatic tumors in several human cancers, thus establishing the principle that a biologic agent working directly on the growth of tumor cells and/or indirectly through the immune system can influence the growth of metastatic tumors and cause tumor regression. The major tumors in which evidence of antitumor activity exists include multiple myeloma, non-Hodgkin's lymphoma, and metastatic breast carcinoma: evidence of tumor regression has been achieved for each type by two or more research groups throughout the world. Future studies of interferon should investigate the precise mechanism of antitumor efficacy, biologic activity, possible tissue specificity, use with other biologic agents, regional therapy, and effects on differentiation. (22 Refs)

65. IMMUNOMODULATION WITH THYMIC HORMONES IN NEOPLASTIC DISORDERS.

Patt YZ
Dept. Developmental Therapeutics, Univ. Texas M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 33(6):265-271 1981

The interaction between thymic hormones and T-cell subsets in neoplastic disorders is discussed. Topics include the endocrine role of the thymus gland, thymosin fraction V, biologic studies with thymosin, thymic humoral factor, facteur thymique serique, thymopoietin II, and the role of thymic hormones in treatment of cancer. Studies with crude thymic extracts should be replaced by studies with well-characterized thymic peptides in well-defined groups of cancer patients. (67 Refs)

66. LYMPHOKINES: THEIR ROLE IN LYMPHOCYTE RESPONSES. PROPERTIES OF INTERLEUKIN 1.

Oppenheim JJ, Stadler BM, Siraganian RP, Mage M, Mathieson B
Lab. Microbiology and Immunology, Natl. Inst. Dental Res., NCI, NIH, Bethesda, MD, 20205
Fed Proc; 41(2):257-262 1982

Interleukin 1, or IL 1, otherwise known as lymphocyte-activating factor, is a macrophage-derived 12,000-to 15,000-dalton polypeptide. Isoelectric focusing of human IL 1 reveals three peaks at pI's of 5.2, 6.0, and 6.9, respectively. IL 1 can be depleted of lymphocyte-derived IL 2 by SP-Sephadex chromatography. IL 1 augments the mitogenic response of PNA- Lyt 1+ thymocytes, and promotes thymocyte helper functions and B cell antibody production. IL 1 induces stable E rosette formation and the production of lymphokines such as T cell growth factor (IL 2) by peripheral T lymphocytes. Others have shown that IL 1 or closely related factors also stimulate hypothalamic cells to induce fever; induce in vitro fibroblast growth, prostaglandin, and collagenase production; and stimulate hepatocytes to produce acute phase proteins such as serum amyloid A. Murine epidermal cells also produce a 15,000-dalton factor that is mitogenic for thymocytes and may be similar to IL 1. We have recently hybridized spleen cells from mice sensitized with partially purified human IL 1 with a myeloma cell line. Clones have been isolated that produce supernatants that partially inhibit the thymocyte proliferative response to IL 1 but not the T cell growth factor activity of IL 2. Should these hybridoma products prove to be monoclonal anti-IL 1 antibodies, they will facilitate the further purification and characterization of IL 1. (Author abstract) (43 Refs)

67. AUGMENTING AGENTS IN CANCER THERAPY.

Hersh EM
Dept. Clinical Immunology and Biological Therapy, Univ. Texas M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 33(6):261-265 1981

Augmenting agents, defined as natural or synthetic materials with the capacity to increase host defense mechanisms nonspecifically by activating host defense cells, are discussed with regard to cancer therapy. After in vivo administration, augmenting agents induce production by increased amounts of lymphokines and cytokines, such as interferon, which activate monocytes, macrophages, and the reticuloendothelial system and which activate natural killer cells and antibody-dependent cell-mediated cytotoxicity. Augmenting agents include intact microbes (BCG, inactivated streptococci OK 432), crude microbial fractions (Staph phage lysates, methanol extraction residue of BCG, cell wall fractions of various organisms), highly purified microbial fractions (peptidoglycans, glycolipids, glucans, lipopolysaccharide), and synthetic agents (pyran copolymer, pyrimidinols, lysolecithin analogs). (31 Refs)

68. ANTITUMOR EFFECT OF TUFTSIN.

Nishioka K, Babcock GF, Phillips JH, Noyes RD
Univ. Texas Health Science Center, Graduate Sch. Biomedical Sciences, Houston, TX, 77030
Mol Cell Biochem; 41:13-18 1981

Tuftsin, a physiological tetrapeptide derived from the Fc region of leukophilic IgG possesses a variety of immunopotentiating properties including the ability to act as an immunotherapeutic agent against the experimental tumors, L1210 leukemia and Cloudman S-91 melanoma. Although the mechanism of action of tuftsin in vivo is not known, several types of leukocytes have been shown to become cytotoxic effector cells following activation with tuftsin. These cells presently include macrophages, natural killer cells, and granulocytes. The possibility that tuftsin can also activate other types of effector cells has not been ruled out. We feel this small peptide has a high potential (largely unrecognized) as a n antitumor immunopotentiating agent. It is naturally occurring in man and appears to be relatively non-toxic. Its exact sequence (Thr-lys-Pro-Arg) is known and it can be chemically synthesized. Methods are also available to monitor the levels of tuftsin in body fluids. These properties along with its ability to control infectious disease make this agent one of the more promising immunopotentiators. (Author abstract) (28 Refs)

69. RECENT DEVELOPMENTS IN THE IMMUNODIAGNOSIS OF CANCER.

Mavligit GM
Dept. Clinical Immunology and Biological Therapy, Univ. Texas M. D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 33(6):250-254 1981

Recent developments in the use of carcinoembryonic antigen (CEA), beta-2-microglobulin, pancreatic carcinoma-associated antigens, prostatic carcinoma-associated markers, miscellaneous tumor-associated antigens, and monoclonal antibodies for immunodiagnosis of cancer are discussed. CEA is useful for early detection of recurrent disease following surgical resection of primary colorectal tumors. The possibility that unnecessary exploratory laparotomies are being performed as a result of more extensive use of serial CEA determinations is discussed; however, serial studies showing a persistent and progressive pattern of rising CEA justify an intensive effort toward tumor localization. Simultaneous determination of beta-2-microglobulin in cerebrospinal fluid and plasma indicates CNS involvement in patients with hematologic malignancies even earlier than the appearance of positive cytology and is used routinely in the total treatment plan of patients with acute leukemia and lymphoma. CEA levels in patients with pancreatic cancer are frequently higher than those in patients with disseminated colorectal cancer. New immunoassays based on pancreatic carcinoma-associated markers are being developed. Radioimmunoassay for prostate acid phosphatase is unlikely to be useful for prostatic carcinoma screening but may be used for more accurate staging. Other tumor-associated antigens include human chorionic gonadotropin, sialoglycoproteins, tissue polypeptide antigen, Tennessee antigen, beta-glucuronidase, and nucleolar antigens. Clinical trials are needed to show whether monoclonal antibodies have any advantage over conventionally prepared antisera in cancer immunodiagnosis. (21 Refs)

70. CHARACTERIZATION OF NORMAL AND MALIGNANT HUMAN LYMPHOID CELL POPULATIONS.

Ford RJ
Dept. Pathology, Univ. Texas M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 33(6):255-260 1981

Characterization of human lymphoid cell populations with both conventional cell membrane markers and monoclonal antibodies is reviewed. The most reliable human T-cell marker is the sheep red blood cell rosette assay, usually performed with neuraminidase-treated sheep RBC. The cell-surface immunoglobulin receptor is the most reliable human B-cell marker; others include the membrane receptor for Epstein-Barr virus and the mouse RBC membrane receptor. Monocytes and macrophages may be identified and separated by means of the phagocytosis of latex particles; in addition, enzymes such as alpha-naphthylacetate esterase are relatively specific for the monocyte/macrophage system when present in a diffuse cytoplasmic staining pattern. Hybridoma technology has given rise to the use of mouse monoclonal antibodies for identifying various types of human lymphocytes. Panels of monoclonal antibodies with defined specificities will probably make conventional cell markers obsolete in the near future. Conventional immunologic markers for a number of neoplastic lymphoid cells, including T- and B-cell lymphomas and leukemias and histiocytic lymphomas, are discussed. Recent studies concerning the use of monoclonal antibodies for differentiation of lymphoma and lymphocytic leukemia subtypes are described. (38 Refs)

71. PLASMA IMMUNOABSORPTION ALTERATION OF HUMORAL IMMUNE COMPONENTS AS A TREATMENT FOR CANCER.

Barnes BC
Dept. Internal Medicine, Medical Breast Service, Univ. Texas M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer Bull; 33(6):278-281 1981

Plasma immunoabsorption as a method for altering humoral response to restore cytolytic function of the immune system is discussed. Tumor-bearing hosts develop increased titers of antitumor antibodies capable of inducing in vivo tumor cell lysis; however, serologic molecules (including IgG subclasses 1, 2, and 3, antiglobulins, circulating tumor antigens, and circulating antibody-antibody complexes) block the humoral response and tumor growth continues. Plasma immunoabsorption can reverse the blocking activity, presumably by complement-mediated tumor cell lysis. The procedure involves separation of plasma from cellular components and absorption of immunoreactive substances from an equilibrium system. The important element of such a system is the absorbent on the column or filter, which must interact with components of the humoral immune system. Animal studies and a clinical trial using a staphylococcal paste layered over a millipore filter resulted in definite antitumor response. Purified protein A bound to solid-phase supports is a newer and safer absorbent, and preliminary studies among breast cancer patients have documented antitumor effects and decreased toxic side effects compared with the staphylococcal system. (27 Refs)

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AUGUST, 1982

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CLINICAL TRIALS

1. TREATMENT OF ACUTE MYELOGENOUS LEUKEMIA: INFLUENCE OF THREE INDUCTION REGIMENS AND MAINTENANCE WITH CHEMOTHERAPY OF BCG IMMUNOTHERAPY.

Omura GA, Vogler R, Lefante J, Silberman H, Knospe W, Gordon D, Jarrell R
Univ. Alabama Birmingham, 638 Zeigler Building, University Station, Birmingham, AL, 35294
Cancer; 49(8):1530-1536 1982

The effect of a synchronizing-recruiting drug schedule vs myelotoxic therapy on remission rate and of Bacillus Calmette-Guerin on remission duration and survival of adults with acute myelogenous leukemia were studied in a prospective cooperative trial. After randomized remission induction with Arabinosyl Cytosine + vincristine + methotrexate + leucovorin (AVML), thioguanine + Ara-C + Daunorubicin (TAD), or Daunobrubicin + Ara-C (DA), complete remissions (CR) were consolidated with TAD or AVML. CRs were maintained with BCG vaccination (Tice strain) by the tine technique, or BCNU plus Ara-C (B/A), or no further therapy (NFT). Of 209 evaluable TAD patients, 105 (50%) achieved CR; of 187 DA, 97 (52%) achieved CR. AVML yielded only 15 CR among 59 patients (25%). The time to remission was significantly shorter with DA compared with TAD. Ninety-seven patients were randomized to maintenance therapy (35 B/A, 30 BCG, 32 NFT). There were no differences in remission duration (7, 8, 6 mo) or survival (16, 22, 16 mo, respectively). Manipulation of the cell cycle, as employed in this study, was not helpful. There may be a marginal effect of BCG, but our data fail to show a statistically significant benefit. (Author abstract) (22 Refs)

2. CLINICAL EVALUATION OF A SYNTHETIC LOW MOLECULAR WEIGHT POLYMER FOR ADVANCED GASTROINTESTINAL CANCER.

Falk RE, Makowka L, Bugala R, Falk JA, Rotstein LE, Ambus U
Room 7344, Medical Sciences Building, Univ. Toronto, Toronto, Ontario M5S 1A8, Canada
Clin Invest Med; 4(3/4):155-159 1981

The polymer NED 137 was administered to 124 subjects with nominally incurable gastrointestinal carcinoma. NED 137 is a synthetic, low mol wt, polycarboxylate copolymer of ethylene and maleic anhydride, with an imide-amide ratio of 3:1 substituted on the polymer backbone. The dose administered to 15 subjects was 30 mg/kg po, to another 15 30 mg/kg ip, and to the rest 5 mg/kg iv to a max of 250 mg. Dosages were repeated every 6 wk; in the 75% of subjects also receiving cytotoxic chemotherapy, NED 137 was given 1-2 wk after a dose of 5-fluorouracil (FU), FU and and mitomycin C (MC), or FU and MC and doxorubicin. The control group consisted of 213 subjects with metastatic gastrointestinal cancer treated with FU or FU and BCG in a previous period at the same institution. A median followup time of 44 wk was achieved for the 114 subjects retained in the study (66% males; mean age 56.3 yr). No toxic or adverse effects derived from the NED 137. Immunological parameters were not altered. Overall, survival in the NED 137 group was improved, especially in a subset of 40 subjects with minimal disease relative to 74 with extensive disease. Subjects having only pancreatic or colon and rectum carcinoma, but not those with stomach carcinoma, survived longer in the NED 137 group. (19 Refs)

3. CYTOREDUCTIVE SURGERY AND SYSTEMIC BACILLUS CALMETTE-GUERIN THERAPY IN METASTATIC RENAL CANCER: A PHASE II TRIAL.

Morales A, Wilson JL, Pater JL, Loeb M
Dept. Urology, Queen's Univ., Victory IV, Kingston General Hosp., Kingston, Onta rio K7L 2V7, Canada
J Urol; 127(2):230-235 1982

A phase II trial has been conducted to determine the effect upon survival of cytoreductive surgery (nephrectomy) and adjuvant active immunotherapy (bacillus Calmette-Guerin) in patients with stage IV renal cancer. A total of 20 patients underwent removal of the primary tumor and received bacillus Calmette-Guerin therapy (adjuvant group). The results were compared to those obtained in 20 historical controls treated with conventional methods (hormones, chemotherapy and radiotherapy with or without nephrectomy) and 16 concurrent controls. All patients in the historical control group were dead within 4 yr after the diagnosis of metastases. Seven patients (35%) in the adjuvant group were alive 2 to 5 yr after documentation of metastatic disease and onset of therapy. The ratio of observed to expected deaths in the adjuvant group was 0.59 compared to 1.6 in historical controls. This superior survival was statistically significant (p less than 0.01). A difference in survival between the adjuvant group and concurrent controls also was present but was not statistically significant (0.10 less than p less than 0.20). Other factors expected to influence survival were investigated. We found that in addition to bacillus Calmette-Guerin therapy a prolonged interval free of disease and better performance status had a better prognosis. Location of metastases, nephrectomy, age and sex are of no significant prognostic value. Definitive answers on the therapeutic value of bacillus Calmette-Guerin and the influence on survival of various biological factors can only be provided by large, controlled, randomized and stratified (phase III) trials. (Author abstract) (32 Refs)

4. COMPLICATIONS OF POSTOPERATIVE INTRAPLEURAL BCG IN LUNG CANCER.

Bakker W, Nijhuis-Heddes JM, De la Riviere AB, Dijkman JH
Dept. Pulmonology and Thoracic Surgery, Univ. Hosp., 10 Rijnsburgerweg, Leyden, The Netherlands
Ann Thorac Surg; 33(3):267-272 1982

Sixty-four patients received BCG intrapleurally following resection for lung cancer. Surgical procedures included segmental resection (3 patients), lobectomy (40), bilobectomy (5), and pneumonectomy (16). BCG was given on the fifth or sixth postoperative day through a chest drain in doses of 16 x 10(6) culturable particles (cp) to 6 patients, 32 x 10(6) cp to 28 patients, and 64 x 10(6) cp to 30 patients. Early side effects (within 2 wk of operation) included elevation of body temperature attributed to BCG in 27 patients (12 receiving the intermediate dose and 13 receiving the highest dose). In general, the temperatures returned to normal within 4-5 days. Late complications attributed to BCG included fever and general malaise which subsided in 2-3 wk in 4 patients, transitory mild liver dysfunction in 2 patients, abscess formation at the site of the BCG drain in 11 patients, wound infection which healed with fistula formation in 2 patients, BCG in the sputum of 1 patient with hemoptysis and pericarditis and of another who developed cavitation, and abnormalities on chest x-rays in 3 patients. Dosage of BCG and preoperative tuberculin response were not related to development of complications. Treatment with isoniazid and rifampin was ineffective. Postoperative intrapleural administration of BCG is a potentially harmful therapy with unproven efficacy. (13 Refs)

5. POSTOPERATIVE INTRAPLEURAL BCG IN LUNG CANCER: LACK OF EFFICACY AND POSSIBLE ENHANCEMENT OF TUMOUR GROWTH.

Bakker W, Nijhuis-Heddes JM, Wever AM, Brutel de la Riviere A, Van der Velde EA, Dijkman JH

Dept. Pulmonology, Univ. Hosp., Leyden, The Netherlands

Thorax; 36(11):870-874 1981

Fifty-six patients out of a group of 99 with lung cancer received postoperative intrapleural BCG (Pasteur strain) in three different dosages (16 x 10(6) culturable particles (cp), 32 x 10(6) cp, and 64 x 10(6) cp). When comparing the whole group of 99 patients with a historical control group of 126 patients no statistically significant differences were found in survival and disease-free interval. The two groups were well matched in respect of age, sex, histology, stage of disease, and type of operation. Patients with epidermoid carcinoma Stage I receiving BCG, however, did significantly worse than those who had not received BCG in terms of disease-free interval. This unfavorable trend was caused by earlier local recurrences rather than metastases. The possible phenomenon of enhanced tumor growth noted in our patients with epidermoid carcinoma Stage I might be related to the dosages used in this study, but the different BCG strain used hinders comparison with other studies. We conclude that BCG has no beneficial effect on survival or on disease-free interval; possible enhancement of tumor growth in Stage I epidermoid carcinoma was found. (Author abstract) (19 Refs)

6. A RANDOMIZED PROSPECTIVE CLINICAL TRIAL OF ADJUVANT C. PARVUM IMMUNOTHERAPY IN 260 PATIENTS WITH CLINICALLY LOCALIZED MELANOMA (STAGE I): PROGNOSTIC FACTORS ANALYSIS AND PRELIMINARY RESULTS OF IMMUNOTHERAPY.

Balch CM, Smalley RV, Bartolucci AA, Burns D, Presant CA, Durant JR, Southeastern Cancer Study Group

Dept. Surgery, Univ. Alabama in Birmingham, University Station, Birmingham, AL, 35294

Cancer; 49(6):1079-1084 1982

A total of 260 patients with clinically localized melanoma (Stage I) from 18 medical institutions in the Southeastern Cancer Study Group were randomized to receive either surgical treatment alone, or surgery plus Corynebacterium parvum immunotherapy. A multivariant analysis (Cox regression model) of nine prognostic factors was performed on 110 patients with a minimum of 2 yr follow-up. The domi nant prognostic variables were thickness ($p = 0.0007$) and anatomic location of the melanoma (trunk vs other, $p = 0.015$). Disease-free survival curves were than calculated for 204 surgically evaluable patients. It is concluded that a prognostic factors analysis is critically important in adjunctive trials of melanoma to determine which dominant variables should be used for analyzing patient subgroups; that C parvum immunotherapy appears to be associated with an improved disease-free survival rate in the subgroup of patients with melanomas greater than 3 mm thickness (this early encouraging data must still be confirmed with continued patients accrual and a longer observation period); and that patients with melanomas less than 3 mm thick have a relatively favorable prognosis after appropriate surgical treatment, and immunotherapy does not improve their survival rates. (24 Refs)

7. EXPERIENCE WITH ADJUVANT CHEMOIMMUNOTHERAPY WITH DTIC AND BCG IN MALIGNANT MELANOMA.

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Z Hautkr; 57(4):294-297 1982

Adjuvant chemoimmunotherapy was tested in 104 patients with malignant melanoma (MM). Forty-four patients had Stage I disease with a high risk (tumor thickness greater than 1.5 mm); 60 patients had Stage II disease. All patients underwent complete excision of tumors and/or metastases. After completion of wound healing patients received 250 mg 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC)/square meter body surface area iv on 5 consecutive days. BCG was injected in increasing doses (0.1, 0.5, 0.5, and 1.0 vaccination doses) 4x in the skin of all four extremities. The treatment cycle was repeated 3x at 4-wk intervals. Side effects included nausea, almost uncontrollable vomiting, and destruction of thrombocytes and WBC. One patient died of Budd-Chiari syndrome. Of patients with Stage I disease receiving DTIC/BCG therapy 91% were alive after 24 mo, including 86% who were free of symptoms. In a control group treated by surgery alone, 85% of patients were alive after 24 mo. Of patients with Stage II disease receiving DTIC/BCG therapy, 33% were alive after 36 mo, including 23% who were free of symptoms. Results indicate no significant improvement in the outcome of treatment with DTIC and BCG over the outcome with surgery alone. (8 Refs) (In GER)

8. PILOT STUDIES USING MELANOMA TUMOR-ASSOCIATED ANTIGENS (TAA) IN SPECIFIC-ACTIVE IMMUNOCHEMOTHERAPY OF MALIGNANT MELANOMA.

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Cancer; 49(7):1387-1404 1982

Highly purified melanoma TAA which induce melanoma-related cell-mediated immune responses have been further characterized using hyperimmune TAA antisera after affinity chromatography for double immunodiffusion-immunoelectrophoresis and indirect immunofluorescence studies. An additional study of antigenic modulation was performed in 23 nonanergic and seven anergic melanoma patients, tested simultaneously with melanoma TAA prepared from primary and metastatic tumors, which had been obtained from one patient at different time periods. The results of pilot clinical trials are reported, including toxicity, timing and dosage studies in 20 patients and subsequent studies of patients with metastatic melanoma treated at three separate centers, using a single lot of purified, allogeneic melanoma TAA. The results of these latter studies in 51 patients with Stage III (distantly metastatic) melanoma and in five patients with earlier stages of disease indicate that: (1) when the interval from primary therapy to recurrence is greater than 1 yr and when liver, bone and brain are not involved, partial or total clinical regression may be noted in up to 25% of patients with metastatic disease receiving immunochemotherapy; (2) when total regression does occur, the effect usually lasts from 1 to 3 yr; (3) cytoreductive (debulking) surgery, when possible, in cutaneous, nodal retroperitoneal, and visceral regions may enhance the response to specific active immunochemotherapy, although some debulked patients had less tumor burden, and this factor alone may lead to an improved prognosis in patients undergoing any subsequently treatment; (4) when circulating inhibitory factors are modified through preimmunization chemotherapy, an enhanced host response may be seen; and (5) Cancer Serum Indices (CSI) may be useful in predicting recurrence and in following tumor load and response to therapy. Information obtained from these studies suggests the need for further trials to determine the effect of immunization on patients with earlier stages of disease where recurrence rates remain high, and to evaluate the mechanisms of tumor rejection or tumor progression in the face of immune stimulation. (Author abstract) (32 Refs)

9. CLINICAL AND IMMUNOLOGIC EFFECTS OF RECOMBINANT LEUKOCYTE A INTERFERON IN EIGHT PATIENTS WITH ADVANCED CANCER.

Horning SJ, Levine JF, Miller RA, Rosenberg SA, Merigan TC
(c/o Merigan) Div. Infectious Diseases, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
JAMA; 247(12):1718-1722 1982

The clinical and immunologic effects of a biosynthetic human leukocyte interferon, recombinant leukocyte A interferon (IFL-rA), are reported in eight patients with advanced cancer. Single escalating doses from 3 x 10(6) units to 198 x 10(6) units were given by intramuscular injection in a Phase 1 study. Major toxic effects included pyrexia, fatigue, myalgia, and headache. Data on the effects of IFL-rA on lymphocyte subpopulations and peripheral blood mononuclear-cell surface beta2-microglobulin are presented. Four of eight patients had objective tumor regression, indicating that further investigation of this biologically active material is warranted. (Author abstract) (25 Refs)

10. DIPHTHERIA TOXIN TREATMENT OF HUMAN ADVANCED CANCER.

Buzzi S
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Cancer Res; 42(5):2054-2058 1982

Purified diphtheria toxin was administered iv to 50 patients with advanced solid tumors. The doses of toxin varied according to the different immunological status of the patients against diphtheria. The prominent toxic effects of the treatment were transient peripheral neuropathy observed in two nonimmune patients and fever (37-41 C) which occurred in all immune patients with cell-mediated hypersensitivity to toxin. A partial response lasting from 2-4 wk was achieved in 3 of 13 nonimmune patients and in 1 of 3 nonimmune patients with cell-mediated hypersensitivity. Of 21 immune patients, 9 had partial response lasting from 4-12 wk. Of 13 immune patients with cell-mediated hypersensitivity, six had partial and five complete response lasting from 2-12 and from 1-25+ mo, respectively. The overall response rate was 48%. The results suggest that diphtheria toxin may have a role in cancer immunotherapy. (Author abstract) (15 Refs)

11. ANTITUMORAL IMMUNOADJUVANTICITY OF PARIETAL SKELETONS OF CANDIDA ALBICANS AND MICROCOCCI.

Favalli C, Baccarini M, Blasi E, Bevilacqua R, Rinaldi C, Mastroviti F
Istituto di Microbiologia, Universita degli Studi di Roma, Roma, Italy
Boll Soc Ital Biol Sper; 57(18):1911-1915 1981

Antitumoral immunoadjuvanticities (IA) of Candida albicans (CA) and Micrococcus lysodeiticus (ML) were evaluated as follows. Parietal insoluble glucan fraction or glucan ghost (GG) was prepared from the CA after repeated extractions with alkalies and acids. Ascitic lymphoma LSTRA was induced in Balb/c mice CD2f1 by Maloney virus. The GG of the CA and the parietal skeletons (PS) of the ML were injected ip 14 days before or 1 day after the tumor transplantation (TT). Effect of the antiblastic agent carmustine (BCNU) was evaluated by administering it 5 days after the TT. Control tests were carried out with inactivated whole cells of the CA. The antitumoral effect was evaluated on the basis of median survival time (MST) and long term survival time (LST: 60 days after the TT), using the Mann-Whitney test. The MST was increased somewhat only with the whole cells of the CA; neither the GG nor the PS had any effect in the absence of the BCNU. The IA was evident in the presence of the BCNU, increasing with dosage (10.8, 18, and 30 mg/kg); this effect was most pronounced when whole cells of the CA were used, with MST of 16%, 30% and 60% and LST of 0%, 25%, and 56% respectively, for the increasing dosages of BCNU . (3 Refs) (In ITA)

12. HUMAN LEUKOCYTE INTERFERON FOR THE TREATMENT OF VARICELLA IN CHILDREN WITH CANCER.

Arvin AM, Kushner JH, Feldman S, Baehner RL, Hammond D, Merigan TC

Dept. Pediatrics, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
N Engl J Med; 306(13):761-765 1982

Results of interferon (IF) treatment of varicella (VA) in children with cancer (CA) are presented. Forty-four patients with CA and VA were enrolled in two consecutive randomized, double-blind placebo-controlled trials. Patients were eligible for the study if they were receiving chemotherapy at the onset of VA or they had received radiation therapy within the preceding mo, and if treatment could be instituted within 72 hr after the appearance of exanthem. Nine of the 18 patients enrolled in the initial trial (1974-1977) received IF at doses of 4.2 x 10(4) to 2.5 x 10(5) units (U)/kg body wt/day until no new vesicles had appeared for 24 hr. The av duration of therapy was 6.4 days. In the second trial (1978-1981) 14 of 26 patients received IF at an initial dose of 3.5 x 10(5) U/kg body wt/day for 48 hr, followed by 1.75 x 10(5) U/kg body wt/day for 72 hr. The IF and placebo groups were compared with respect to underlying disease, number of days from onset of VA to enrollment in the study, number of lesions at entry, and initial white-cell and platelet counts. Sixteen of 23 IF recipients and 14/21 placebo recipients had acute lymphocytic leukemia. Treatment with IF had a significant effect on the number of days of new lesion formation in immunocompromised patients with VA. Ninety percent of IF recipients had no new lesions for at least 24 hr by day 7 after enrollment, compared with 56% of placebo recipients. The overall incidence of fatal and life-threatening VA was 8.7% (2/23) in the IF group and 28.6% (6/21) in the placebo group. Results indicate that IF has an antiviral effect against VA virus in immunocompromised patients. (13 Refs)

INTERFERON

13. STUDIES OF THE FUNCTIONS OF NATURAL KILLER-INTERFERON SYSTEM IN PATIENTS WITH SJOGREN SYNDROME.

Minato N, Takeda A, Kano S, Takaku F
Div. Clinical Immunology, Dept. Medicine, Jichi Medical Sch., Tochigi 32904, Japan
J Clin Invest; 69(3):581-588 1982

The natural killer (NK)-interferon (IFN) system is shown to be significantly involved in the resistance of host to viral infections and to tumors in numbers of animal models. The patients with Sjogren syndrome (SS) as well as those with collagen diseases were systematically investigated for the functions of NK-IFN system, including endogenous and augmented NK activity, IFN production, and responsiveness of NK cells to IFN stimulation, using virus persistently infected cells (HeLa-measles cells) as target and stimulator cells. Although endogenous NK activity was not reduced, augmented NK activity by HeLa-measles cells in vitro was significantly depressed in patients with SS compared with that in age-matched normal controls. The patients with SS had also impaired capacity to produce IFN, which is shown to be a major factor regulating NK activity in response to HeLa-measles cells in vitro. In three patients with SS who showed severely depressed NK activity, the effect of exogenous IFN was examined, and virtually no augmentation of NK activity was observed in all cases. Under the same condition, the normal controls demonstrated a dramatic increase in NK activity. The reduced IFN production was observed in all examined patients with SS, whereas impaired augmentation of NK activity by the stimulation with HeLa-measles cells as well as IFN seemed to be more striking in patients with the systemic manifestations of the disease, such as hypergammaglobulinemia and lymphoid hyperplasia. The possible involvement of dysfunction of NK-IFN system in the systemic manifestations of SS is discussed. (Author abstract) (35 Refs)

14. SERUM SEX STEROID AND PEPTIDE HORMONE CONCENTRATIONS, AND ENDOMETRIAL ESTROGEN AND PROGESTIN RECEPTOR LEVELS DURING ADMINISTRATION OF HUMAN LEUKOCYTE INTERFERON.

Kauppila A, Cantell K, Janne O, Kokko E, Vihko R
Population Council, New York, NY
Int J Cancer; 29(3):291-294 1982

Five normally cycling healthy women were given daily sc injections of human leukocyte interferon (3 x 10(6) units/day) from the 3rd through 23rd day of the menstrual cycle, and serum steroid and peptide hormone concentrations monitored at 3-day intervals during the treatment and the preceding control cycle. Concentrations of cytosol and nuclear estrogen receptors (ERc and ERn, respectively) and progestin receptors (PRc and PRn) were also measured from endometrial biopsies taken on the 24th day of the control and treatment cycle. In addition, an extensive monitoring of clinical chemical and hematological tests from the blood samples were performed. Serum estradiol and progesterone concentrations were significantly decreased during the treatment cycle, suggesting that interferon interacts in vivo with the function of both FSH and LH. No significant changes were observed in the serum peptide hormone concentrations measured (FSH, LH, prolactin, insulin, growth hormone and TSH); neither were the levels of endometrial ERc, ERn, PRc and PRn affected by interferon administration. As expected, interferon administration resulted in decreased leukocyte counts. Moreover, an increasing tendency in the activities of serum alkaline phosphatase and gamma-glutamyltransferase during the interferon therapy shows that interferon may slightly interfere with the liver function. These results suggest that one of the mechanisms by which interferon treatment may affect the growth of hormone-dependent neoplasms could be the interaction with production and/or function of circulating hormonal compounds. (Author abstract) (15 Refs)

15. HUMAN LEUKOCYTE INTERFERON-MEDIATED GRANULOPOIETIC DIFFERENTIATION ARREST AND ITS ABROGATION BY LITHIUM CARBONATE.

Verma DS, Spitzer G, Gutterman JU, Beran M, Zander AR, McCredie KB

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Am J Hematol; 12(1):39-46 1982

Interferon has been shown to inhibit erythropoietic and granulopoietic differentiation. Since lithium carbonate (Li) elevates granulocyte levels in a variety of neutropenic disorders, we investigated the effect of Li on human leukocyte interferon (HLIF)-mediated inhibition of granulopoietic differentiation. Using an agar culture technique for cloning granulocyte-macrophage progenitor cells (GM-CFC), we demonstrated that Li blocks HLIF-induced granulopoietic differentiation arrest in a dose-dependent manner. Results of removal of T lymphocytes from marrow cells suggest that this Li effect is not mediated through marrow T lymphocytes. (Author abstract) (17 Refs)

16. HISTOPATHOLOGIC AND HISTOENZYMATIC OBSERVATIONS IN CARCINOMAS TREATED WITH HUMAN LEUKOCYTE INTERFERON.

Knezevic M, Knezevic-Krivak S, Ikic D, Maricic Z, Krusic J, Padovan I, Nola P, Brodarec I, Jusic D, Soos E

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Int J Clin Pharmacol Ther Toxicol; 20(1):27-38 1982

Histologic and histochemical examination of the bioptic material of 34 cases of uterocervical carcinoma (UCC) and 30 cases of head and neck tumors treated with crude human leukocyte interferon (HLI) revealed excellent positive response for both types of disease. The UCC patients showed a positive response to therapy in 70% of the cases. The principal reason for nonresponse was evidently failure of interferon to penetrate deeply through the mucosa into extensive tumor growths. HLI significantly enhanced the spontaneous peritumoral defense of tissue in cases of carcinoma microinvasivum and carcinoma in situ. In the cases of carcinoma of the skin, lips, and oral cavity, interferon definitely had a positive effect in 80%, a healing effect in 50%, and a very likely healing effect in an additional 25%. HLI stimulated the infiltration of stroma with the masses of lymphocytes and macrophages. Macrophages showed signs of increased activity, and new lymph nodules were observed at the site of the tumor. (22 Refs)

17. THE ACTIVITY OF INTERFERON ON ULTRAVIOLET LIGHT-INDUCED SQUAMOUS CELL CARCINOMAS IN MICE.

Brysk MM, Tschen EH, Hudson RD, Smith EB, Fleischmann WR, Black HS
Dept. Dermatology, Univ. Texas Medical Branch, Galveston, TX, 77550
J Am Acad Dermatol; 5(1):61-63 1981

Effects of virus type (VT: IF-alpha + IF-beta) and immune (I: IF-gamma) interferons (IF) used separately or in combination on epidermal tumors induced by UV light in albino hairless mice (SKH-Hv-1) were investigated. Mice were exposed to UV light (1.13 joules/square cm (cm2)/day initially to 1.97 joules/cm2/day through 16 wk). Eighteen tumors (squamous cell carcinomas) on nine mice were injected intralesionally with 3,000 units/site of VT-IF/day, 16 tumors on 9 animals received 10 units/site I-IF/day, 19 tumors on 9 mice received combined IF (3,000 units VT-IF and 10 units I-IF/site/day), and 19 control tumors on 10 mice received mock IF. No systemic effects of IF were observed. Results with I-IF were similar to those with mock IF. Tumor regression with VT-IF was greater than in controls, but the difference was not significant. Regression in the group receiving combined IF treatment was significantly greater than in controls. Thus, antitumor activity was enhanced by combining the two IF types, even though each IF was ineffective when used alone. (11 Refs)

18. ANTITUMOR EFFECT OF COMBINED INTERFERON AND HYPERTHERMIA IN MICE.

Yerushalmi A, Tovey MG, Gresser I
Radiation Unit, Weizmann Inst. Science, Rehovot, Israel
Proc Soc Exp Biol Med; 169(3):413-415 1982

The effect of hyperthermia and interferon (INF) was tested in C57B1/6 mice bearing transplantable Lewis lung carcinoma. Combined therapy with either exogenous INF or INF inducers (polyinosinic-polycytidylic acid or Newcastle disease virus) together with local hyperthermia had a greater antitumor effect than either treatment alone. (15 Refs)

19. EFFECT OF HUMAN RECOMBINANT INTERFERON ON CYTOTOXIC ACTIVITY OF NATURAL KILLER (NK) CELLS AND MONOCYTES.

Herberman RB, Ortaldo JR, Mantovani A, Hobbs DS, Kung HF, Pestka S
Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD, 20205
Cell Immunol; 67(1):160-167 1982

Studies have been performed on the in vitro immunologic effects of homogeneous recombinant human leukocyte interferon, IFLrA. Large granular lymphocytes, enriched for natural killer (NK) cell activity, were pretreated with IFLrA or natural interferon preparations and then tested for augmentation of NK activity and of antibody-dependent cell-mediated cytoxicity (ADCC). Monocytes were tested for cytolytic and cytostatic activity in 48-72 hr radioisotopic assays performed in the presence or absence of interferon. Treatment with IFLrA caused significant augmentation of NK, ADCC, and monocyte-mediated cytotoxic activities. Even 10 units of IFLrA induced augmentation of NK activity, and 100 units or more boosted monocyte-mediated activity. The effects in each of these assays were species-specific, with no detectable effects on the activity of mouse effector cells. These results indicate that homogeneous recombinant interferon has potent in vitro immunomodulating effects and thus provide a basis for carefully examining the in vivo effects of this protein on host defenses in forthcoming clinical trials with cancer patients. (Author abstract) (43 Refs)

20. CELL GROWTH REGULATION DURING DENSITY INHIBITION AND INTERFERON TREATMENT.

Leandersson T, Lundgren E
Lab. Cell and Tissue Culture Res., Univ. Umea, S-901 87 Umea, Sweden
Exp Cell Res; 138(1):167-174 1982

The growth of P3HR-1, a Burkitt's lymphoma cell line, was regulated differently at high cell numbers and upon treatment with human leukocyte interferon (IFN-alpha). At terminal cell titer, cell growth was reduced by progressing through the cell cycle more slowly, whereas IFN-treated cells escaped from the cell cycle by going into a G0-like state. Furthermore, in comparison with density-inhibited cells, IFN-treated cells had, upon dilution into fresh medium, a longer lag period before they began to grow exponentially again. No G0/G1 restriction point was apparent in this cell line. These cells had to undergo one mitotic division before any IFN-induced inhibition of proliferation could be observed. (Author abstract) (19 Refs)

21. POTENTIATION OF THE DIRECT ANTICELLULAR ACTIVITY OF MOUSE INTERFERONS: MUTUAL SYNERGISM AND INTERFERON CONCENTRATION DEPENDENCE.

Fleischmann WR
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Cancer Res; 42(3):869-875 1982

Mouse immune (IFN-gamma)2 and virus-type (IFN-alpha/beta) interferons were used separately and in combination in cloning studies with B-16 melanoma cells. IFN-gamma was found to be a more potent mediator of the direct anticellular effect of interferon than was IFN-alpha/beta, as shown not only by a greater sensitivity of B-16 cells to IFN-gamma but also by a steeper slope of the anticellular sensitivity curve of the IFN-gamma. The differences in the slopes of the curves defining their anticellular effect appeared to be inherent in the interferons themselves and not due to an inhibitor of interferon, a stimulator of cell growth, or another factor possessing anticellular activity. The results are consistent with the interpretation that IFN-gamma and IFN-alpha/beta exert their anticellular effects by different mechanisms. The anticellular activity of interferon against B-16 melanoma replication unit development was potentiated by mixed preparations of IFN-gamma and IFN-alpha/beta. The potentiation appeared to be an expression of a property of the interferons themselves. Replication units resistant to the potentiated activity of the interferons were not detected. Potentiation levels were dependent on the concentrations of both IFN-gamma and IFN-alpha/beta and continued to increase dramatically as the interferon concentrations increased. Max potentiation observed was 214-fold at the highest interferon concentrations used. The data suggest that potentiation is a mutual, synergistic interaction of IFN-gamma and IFN-alpha/beta. (Author abstract) (22 Refs)

22. DIFFERENT SUSCEPTIBILITIES OF CULTURED MOUSE CELL LINES TO MOUSE INTERFERON.

Tsuruo T, Iida H, Tsukagoshi S, Oku T, Kishida T
Center Chemotherapy Center, Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan
Gan; 73(1):42-47 1982

Cultured mouse cells were treated with 3.3 to approx 10,000 units of mouse interferon for 3 days and further cultivated in fresh medium for 2 days (recovery incubation). The IC50 (concentration of drug required for 50% inhibition) of interferon was not changed much after the recovery incubation. The most susceptible cell line to interferon was B16 melanoma; the IC50 was 10.5 units per ml of medium on day 3 after the start of treatment. P388 leukemic cells, Lewis lung carcinoma cells, and colon adenocarcinoma 38 cells were moderately susceptible to interferon and the IC50s of these cell lines were 200, 80, and 180 units per ml medium, respectively, on day 3. The cells least susceptible to interferon were those of colon adenocarcinoma 26; IC50 was greater than 10,000 units per ml. In the recovery incubation, the growth of B16 melanoma cells, P388 leukemic cells, Lewis lung carcinoma cells and colon adenocarcinoma 38 cells was considerably inhibited when these cells were treated with more than 100 to approx 1,000 units of interferon per ml medium. The rate of multiplication was usually more than 1 for these cell lines, except for Lewis lung carcinoma cells where the rate of multiplication was less than 1. This indicates that interferon is not cytocidal towards B16 melanoma cells, P388 leukemic cells, or colon adenocarcinoma 38 cells, but mouse interferon is cytocidal towards Lewis lung carcinoma cells when the cells were treated with a relatively high concentration of interferon and then cultured in the medium without interferon. (Author abstract) (23 Refs)

23. MODULATION OF NATURAL KILLER SENSITIVITY OF MURINE TROPHOBLAST CELLS BY TUMOR PROMOTER AND INTERFERON.

Tanaka K, Chang KS
Lab. Cell Biology, NCI, Bethesda, MD, 20205
Int J Cancer; 29(3):315-321 1982

The in vitro established lines of murine placental trophoblast cells showed little membrane expression of H-2 antigens and a high degree of sensitivity to natural killer (NK)-cell-mediated cytotoxicity. This NK-sensitivity was decreased either by short-term treatment of these cells with murine interferon (IFN) or by culture for more than 4 days in the presence of a tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA). This effect of TPA was reversible after removal of TPA from the culture medium. However, IFN treatment of trophoblast cells cultured previously in TPA medium resulted in restoration of NK-sensitivity to the original level exhibited by cells untreated with IFN or TPA. The mechanism for this antagonistic effect is not clear. The decrease in NK-sensitivity of IFN- or TPA-treated trophoblast cells was not due to the loss of NK-recognition membrane structures, or to induction of prostaglandin which elevates cyclic-AMP levels. Inhibition of protein synthesis by cycloheximide restored the NK-sensitivity of TPA-treated trophoblast cells, indicating the possible contribution of de novo synthesized protein(s) which could confer NK-resistance. The TPA-treated trophoblast cells became more tumorigenic, producing larger tumors and a higher mortality than the untreated controls when inoculated into mice. The possible roles of NK cells in trophoblastic diseases and fetomaternal relationships are discussed. (Author abstract) (27 Refs)

24. CELLULAR REGULATION OF GAMMA INTERFERON PRODUCTION: LYT PHENOTYPE OF THE SUPPRESSOR CELL.

Torres BA, Yamamoto JK, Johnson HM
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Infect Immun; 35(3):770-776 1982

Suppressor cell activity for in vitro gamma interferon (IFN-gamma) production can be induced in C57BL/6 mice with staphylococcal enterotoxin A and concanavalin A. The suppressor cell lacked mitogen specificity. The IFNgamma-producing cell has a low density of Thy 1. Monoclonal anti-Lyt 2.2 antibody completely eliminated the suppressor cell activity, whereas anti-lyt 1.2 partially reduced the suppressor cell activity. The suppressor cell may be or may require a Lyt 1,2,3+ cell with a relatively low density of the Lyt 1 antigen for activity. Treatment of cells with either anti-Lyt 1.2 or anti-Lyt 2.2 completely eliminated IFNgamma production in both virgin and suppressor cell cultures. Cocultivation of Lyt 1+ and Lyt 2+ cells in both virgin and suppressor cell cultures restored the ability to produce IFNgamma when cells were stimulated with staphylococcal enterotoxin A. For the virgin cells, this seems to indicate clearly that both Lyt 1+ and Lyt 2+ cells are required for IFN production, but that Lyt 1,2,3+ cells are not required. For the suppressor cell population this type of treatment resulted in IFNgamma production comparable to that of the virgin cell population. The treatment eliminated or depleted Lyt 1,2,3+ cells from the suppressor cell population, thus providing additional evidence that a Lyt 1,2,3+ cell is required for suppressor cell activity. Treatment of spleen cells with anti-Lyt antibodies at the time that they were involved in ongoing IFNgamma production showed that the IFNgamma-producing cell is Lyt 2+. A 1:1 ratio of virgin to suppressor cells was required for suppression of IFNgamma production by virgin spleen cells. Preliminary data showed that the suppressor cell activity could be induced in in vitro cultures incubated with mitogen for 4 days. This is evidence that the suppressor cell is inducible and not necessarily recruited to the spleen from other lymphoid organs. (Author abstract) (22 Refs)

25. ACTIVATION OF NATURAL KILLER CELLS AND INDUCTION OF INTERFERON AFTER INJECTION OF MOUSE HEPATITIS VIRUS TYPE 3 IN MICE.

Schindler L, Engler H, Kirchner H

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Infect Immun; 35(3):869-873 1982

High levels of natural killer (NK) cell activity and high titers of interferon were observed in the peritoneal exudate of C57BL/6 mice 20 to 50 h after injection of mouse hepatitis virus Type 3 (MHV3) but not during the first 10 h after infection. C57BL/6 mice were susceptible to MHV3 infection and showed high titers of MHV3 in the peritoneal exudate 48 h after infection. A/J mice, in contrast, were resistant to the dose that killed 100% of the C57BL/6 mice (10 macrophage-infecting doses) and showed considerably lower virus titers than those shown by C57BL/6 mice. NK cell activity and interferon titers were significantly lower in the peritoneal exudate of A/J mice than in that of C57BL/6 mice. Serum interferon titers were also lower in A/J mice. Thus, our data show an inverse relationship between resistance and the levels of these two parameters. The data suggest that, in contrast to the situation observed with certain herpesviruses, interferon and NK cells may not be of overwhelming importance in the defense of mice against MNV3. (Author abstract) (14 Refs)

26. EFFECT OF INTERFERON ON THE EXOGENOUS FRIEND MURINE LEUKEMIA VIRUS INFECTION.

Riggin CH, Pitha PM
(c/o Pitha), Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21218
Virology; 118(1):202-213 1982

Interferon treatment (600 U/ml) of NIH/3T3 cells induced greater than 90% reduction in the de novo production of Friend MuLV when measured 24 hr postinfection. Early events in viral replication such as the synthesis of proviral DNA and its subsequent integration into the cell genome were not inhibited by interferon treatment indicating that the suppression of virus production by interferon appears to occur after synthesis of proviral DNA. Analysis of viral RNA species present in controls and interferon-treated cells 24 hr after infection show that the same RNA species were present in the presence and absence of interferon. Synthesis of viral polypeptides was reduced but not blocked in interferon-treated cells when measured within 24 hr after infection while processing of gag precursor, Pr65gag, and glycoprotein precursor, gPr85env, to viral proteins was not altered. Phosphorylation of viral protein p12 but not that of the precursor, Pr65gag, was inhibited in newly infected interferon-treated cells. In contrast to the first replicative cycle, interferon did not inhibit synthesis of viral proteins, and phosphorylation of p12 in those cells chronically infected with F-MuLV. (Author abstract) (32 Refs)

27. PROTECTION OF NEWBORN MICE FROM A LETHAL HERPES SIMPLEX VIRUS INFECTION BY HUMAN INTERFERON, ANTIBODY, AND LEUKOCYTES.

Kohl S, Loo LS, Greenberg SB
Program Infectious Diseases, Univ. Texas Medical Sch., P.O. Box 20708, Houston, TX, 77025
J Immunol; 128(3):1107-1111 1982

Newborn mice infected ip with a lethal dose of herpes simplex virus (HSV) were protected by a combination of human interferon and human mononuclear cells (MC) when it was administered ip 1 day before infection (35.2% survived, p less than 0.001). The HSV immune status of the MC donors did not affect this protection. The number of MC required in the presence of 100 units of interferon was 5 x 10(6) to 5 x 10(5)/ mouse. The dose of interferon required in the presence of 5 x 10(6) MC was 100 to 10 U. Highest survival was achieved with 5 x 10(6) MC and 100 U of interferon. The active human effector cell in this system was either a lymphocyte or a monocyte-macrophage but not a polymorphonuclear leukocyte. Treatment of mice with interferon and MC after viral inoculation was not successful. Protection by human WISH cells (a non-leukocyte) and interferon was demonstrated (55% survival, p less than 0.001), which suggested that protection was due to interferon induced cross-species active antiviral protein production. The human interferon stimulated human but not murine or WISH cell natural killer cytotoxicity (NKC) in vitro. Mice receiving human interferon, MC, and subneutralizing doses of anti-HSV antibody before HSV infection were almost completely (95.2%) protected, and were protected significantly better (p less than 0.001) than mice receiving either MC plus interferon or MC plus antibody. Although adult MC could mediate this protection, all mice receiving MC from neonatal humans plus antibody and interferon died (p less than 0.001). In vitro experiments showed that protection was not due to viral neutralization. This is the first evidence for either in vivo human antiviral NKC or cross-species antiviral protein protection as well as defective in vivo human neonatal MC function in this system. (Author abstract) (29 Refs)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

28. EFFECT OF BACILLE CALMETTE-GEURIN IMMUNOTHERAPY ON FELINE SARCOMA VIRUS-INDUCED NEOPLASMS IN THE CAT.

Bachman D, Cockerell GL, De Noronha F, Rapp HJ
Dept. Pathology, New York State Coll. Veterinary Medicine, Cornell Univ., Ithaca, NY, 14853
Am J Vet Res; 43(3):475-480 1982

Kittens infected experimentally with feline sarcoma virus (FeSV) were inoculated with emulsions of bacille Calmette-Guerin (BCG) cell wall preparations to determine the effect of BCG immunotherapy on FeSV-induced sarcomagenesis. The BCG preparations or emulsificant control preparations were administered (i) subcutaneously at the same time and site as was the FeSV inoculation, (ii) at the same site but 1 wk after FeSV inoculation, or (iii) with a mixture of viable autochthonous neoplastic cells approx 35 days after FeSV inoculation. There was no difference in the percentage of kittens that developed neoplasms, the prepatent period for neoplastic development, the percentage of kittens with neoplastic regression, or the survival rate among groups given BCG, emulsificant control, or FeSV alone. Significantly (p less than 0.05) greater dissemination of neoplasms was seen in groups given BCG or emulsificant control preparations, compared with dissemination in groups given FeSV alone. (Author abstract) (25 Refs)

29. THE RELATIONSHIP BETWEEN COMPETENCE FOR SECRETION OF H2O2 AND COMPLETION OF TUMOR CYTOTOXICITY BY BCG-ELICITED MURINE MACROPHAGES.

Cohen MS, Taffet SM, Adams DO
(c/o Adams) Dept. Pathology, Duke Univ. Medical Center, Durham, NC
J Immunol; 128(4):1781-1785 1982

BCG-elicited macrophages from C3H/HeJ and A/J mice secrete H2O2 comparably to BCG-elicited macrophages from control C3H/FeJ mice in response to the pharmacologic stimulant phorbol myristate acetate. By contrast, BCG-elicited macrophages from C3H/HeJ and A/J mice could not effect tumor cytotoxicity, whereas macrophages from the control C3H/FeJ mice could. When BCG-activated macrophages from C57BL/6J mice were held in culture overnight, their ability to secrete H2O2 in response to the pharmacologic trigger declined 40 to 60%; the presence of endotoxin in the overnight cultures did not alter competence for secretion of H2O2. By contrast, the cultured macrophages lost all of their cytolytic competence, but this competence could be fully maintained by the presence of endotoxin in the cultures. In three distinct circumstances, competence for secretion of H2O2 thus did not correlate with competence for completion of tumor cytotoxicity. The data imply that competence for release of H2O2 is not sufficient for completion of tumor cytotoxicity. (Author abstract) (37 Refs)

30. IMMUNOGENETICS OF BCG-INDUCED ANERGY IN MICE; CONTROL BY GENES LINKED TO THE IGH COMPLEX.

Schrier DJ, Sternick JL, Allen EM, Moore VL
(c/o Moore) Res. Service/151, Veterans Admin. Medical Center, Wood, WI, 53193
J Immunol; 128(3):1466-1469 1982

The genetics of BCG-induced anergy was studied in mice by evaluating delayed hypersensitivity to sheep erythrocytes. Data obtained using congenic mice and by linkage analysis suggested that genes linked to the H-2 complex do not influence the development of anergy. However, studies in allotype-congenic partners (BALB/c; BALB.Igb) indicated that anergy was influenced by genes linked to the immunoglobulin heavy chain complex (Igh). Breeding studies indicated that the gene influencing anergy is recessive. These studies were extended by using BXD recombinant inbred mice and verified that anergy is controlled by genes linked to the Igh complex. Because several markers and a tentative map have been constructed for the Igh complex on chromosome 12 in BXD mice, we suggest that the gene that controls BCG-induced anergy is located on the centrometric side of Igh-C approximately 18 to 28 recombination units. (Author abstract) (40 Refs)

31. CELL-MEDIATED IMMUNITY IN MALNOURISHED GUINEA PIGS AFTER MYCOBACTERIUM BOVIS BCG VACCINATION.

McMurray DN, Yetley EA
Dept. Medical Microbiology, Texas A and M Univ., College Station, TX, 77843
Infect Immun; 35(3):909-914 1982

Specific-pathogen-free guinea pigs were vaccinated with viable Mycobacterium bovis BCG and maintained on purified, isocaloric diets containing either 30% or 7.5% casein, or commercial chow. At intervals of 4, 5, 6, and 8 weeks postvaccination, groups of guinea pigs from each diet treatment were skin tested with purified protein derivative and killed. Protein-deficient animals exhibited progressive reductions in total serum proteins and albumin. Significantly greater numbers of viable M bovis BCG were recovered from the vaccination site and inguinal lymph nodes of protein-deficient guinea pigs at all intervals. In contrast, the development of delayed hypersensitivity was markedly retarded in the 7.5% casein group and was also reduced somewhat in the 30% casein group as compared to chow control. Peripheral blood lymphocytes from protein-deficient animals did not respond normally in vitro to a polyclonal T cell mitogen, phytohemagglutinin. These results demonstrate that protein-calorie malnutrition in this model impairs the development of cell-mediated immunity as evidenced by skin test anergy, lymphocyte hyporesponsiveness, and failure to control levels of viable M bovis BCG after vaccination. (Author abstract) (34 Refs)

32. IN VITRO ACTIVITY OF NK-CELLS FROM C57BL/6 MICE IRRADIATED AND IMMUNOSTIMULATED BY CORYNEBACTERIUM PARVUM.

Badea E, Corneci I, Rozescu B
Oncological Inst. Bucharest, Bucharest, Romania
Rev Chir [Oncol]; 20(3):185-191 1981

The in vitro activity of natural killer cells (NK) was studied after irradiation and/or stimulation of the donor animal with Corynebacterium parvum. Adult male and female C57BL/6 mice were exposed to 500 rad x-rays. Various groups received 2.0-2.5 mg dried C parvum injected ip 30, 14, 7, 5, or 3 days or 1 hr before irradiation or 1 hr or 3 days after irradiation. Mice were killed 9 days after irradiation and splenocytes and peripheral blood cells were obtained. NK activity was analyzed against syngeneic (Lewis tumor growing in C57BL/6 mice), allogeneic (Ehrlich ascites growing in A strain mice), and xenogeneic (B1R ascites and MC fibrosarcoma growing in R strain rats) tumor cells. An av spontaneous NK cytotoxicity of 27% was observed. Irradiation reduced NK activity to 21%, indicating that NK are relatively radioresistant. NK activity did not vary significantly with the sex of the donor or with the type of target cell. C parvum inoculation stimulated macrophage production. However, removal of macrophages did not affect NK activity, indicating that macrophages do not affect the promotion phase of NK. C parvum inoculation produced the greatest NK activity 4 days after inoculation. NK activity declined after day 4 but remained elevated 6-12 days longer. (22 Refs)

33. INHIBITION OF EXPERIMENTAL TUMOR METASTASIS BY SELECTIVE ACTIVATION OF NATURAL KILLER CELLS.

Hanna N
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Cancer Res; 42(4):1337-1342 1982

The antitumor activity generated by selective activation of natural killer (NK) cells was studied in vitro and in vivo. Unlike Corynebacterium parvum CN6134, which activated both NK cells and macrophages, periodate-oxidized C parvum CN6134 lost the ability to activate macrophages but retained almost all the NK-stimulating capacity of the untreated bacterium. The 'inactive' C parvum strain CN5888 also induced a modest, but selective, activation of NK cells. The enhanced NK cell-mediated cytotoxicity was expressed against YAC-1 lymphoma, UV-2237 fibrosarcoma, and B16 melanoma target cells in vitro and was manifested in vivo by increased destruction of circulating tumor cells and the inhibition of hematogenous tumor metastasis. Periodate-treated C parvum was as effective in inhibiting the formation of B16 melanoma pulmonary metastases as was untreated C parvum. In both cases, the inhibiting effect corresponded closely with the kinetics of NK cell activation. (Author abstract) (28 Refs)

34. CIMETIDINE AMPLIFIES THE ANTI-NEOPLASTIC EFFECT OF TRICHINELLA SPIRALIS IN MICE.

Ruitenberg EJ, Kruizinga W, Steerenberg PA, Elgersma A, De Jong WH
Lab. Pathology, Natl. Inst. Public Health, Bilthoven, The Netherlands
Br J Cancer; 45(2):314-316 1982

The possible involvement of histamine in the antineoplastic effect of Trichinella spiralis on growth of a murine fibrosarcoma (induced by 3-methylcholanthrene) was investigated. An H2-receptor antagonist (cimetidine) and an H2-receptor agonist (tolazoline) were used. Inbred female BALB/c mice were infected orally with 200 T spiralis larvae 8 days before sc inoculation of 5 x 10(5) tumor cells into the footpad. Cimetidine (50 mg/kg) or tolazoline HCl (0.5 mg/kg) was administered ip on days-8,-6,-4,-2, and 0. Preinfection with 200 T spiralis larvae retarded tumor growth as early as 5 days after tumor cell inoculation. Cimetidine caused an additional tumor growth retardation visible from day 5. Tolazoline did not affect tumor retardation induced by T spiralis. Neither drug alone affected tumor growth. The antitumor effect of T spiralis may be modulated by parasite-induced suppressor T cells, known to possess H2-

receptors, whose effect is blocked by cimetidine. The potential of cimetidine in regulating immune responses, including its role in cancer immunotherapy, is implied by the findings. (8 Refs)

MICROBIAL FRACTIONS AND EXTRACTS

35. CANINE OSTEOGENIC SARCOMA TREATED BY AMPUTATION AND MER: AN ADVERSE EFFECT OF SPLENECTOMY ON SURVIVAL.

Meyer JA, Dueland RT, MacEwen G, Macy DW, Hoefle WD, Richardson RC, Alexander JW, Trotter E, Hause WR

750 E. Adams St., Syracuse, NY, 13210

Cancer; 49(8):1613-1616 1982

Canine and human osteogenic sarcomas, like most other malignant tumors, cause or are associated with progressive impairment of host immune reactivity. Adjuvant immunotherapy with live BCG had shown increased survival in one study of canine disease. Experiments with induced fibrosarcomas in mice had suggested that some of the host immune defect might be ameliorated by splenectomy. A prospective clinical trial was conducted with several cooperating veterinary centers. Dogs with osteosarcoma apparently confined to a limb were randomized to be treated by amputation and methanol-extracted residue of BCG (MER), or by the same modalities plus splenectomy. Randomization was discontinued relatively early in the study because of higher mortality in the splenectomy group. Animals treated by amputation and MER could be compared only with historic controls; median and 1-yr survival rates did not differ significantly from those of prior series. Animals treated by amputation, splenectomy, and MER had significantly poorer survival. (Author abstract) (15 Refs)

36. EFFECTS OF ENDOTOXIN ON MURINE ERYTHROPOIESIS IN VITRO: ROLE OF MARROW ADHERENT CELLS.

Anagnostou A, Poloii-Anagnostou L, Schade S

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J Reticuloendothel Soc; 31(2):145-154 1982

Endotoxin injected into experimental mice suppresses marrow erythropoiesis by an as yet unknown mechanism. We have studied the effects of endotoxin added to the methylcellulose culture system for growth of erythroid stem cells (BFU-E). The addition of endotoxin decreased BFU-E growth from murine normal (unseparated) femoral marrow mononuclear cells. This suppressive effect was not seen when most of the adherent cells were removed from the culture system prior to the addition of endotoxin. We speculate that whereas 'normal' adherent cells provide a favorable microenvironment for the growth of erythroid stem cells, adherent cells altered by endotoxin either lose their ability to support erythroid growth or suppress erythroid colony formation. These observations may be of relevance to the explanation of the pathogenesis of the anemia of infection or chronic disease. (Author abstract) (25 Refs)

CYTOKINE THERAPY

37. PREVENTION OF THE IN VITRO MYELOSUPPRESSIVE EFFECTS OF GLUCOCORTICOSTEROIDS BY INTERLEUKIN 1 (IL 1).

Mishell RI, Lee DA, Grabstein KH, Lachman LB
Dept. Microbiology and Immunology, Univ. California, Berkeley, CA, 94720
J Immunol; 128(4):1614-1619 1982

We investigated the effects of dexamethasone on the formation of granulocyte/macrophage colonies by murine bone marrow cells cultured with colony-stimulatory factors (CSF) in semisolid agar. Dexamethasone (10-7M) completely inhibited the formation of colonies in response to L929 CSF but had no effect on the response to CSF in the culture supernatants of the murine macrophage cell line, PU5-1.8. We postulated that a cofactor, interleukin 1, present in the PU5-1.8 supernatants was responsible for protecting colony formation against steroid suppression. Interleukin 1, isolated from culture supernatants of PU5-1.8 and from culture supernatants of human acute monocytic leukemia cells, blocked the inhibitory effects of dexamethasone on colony formation in response to L929 CSF. Moreover, dexamethasone inhibited colony formation in response to PU5-1.8 culture supernatants when interleukin 1 was absent. We also examined interleukin 2 for possible protective effects. Although crude interleukin 2 preparations (supernatants of spleen cells cultured with concanavalin A) blocked dexamethasone inhibition, purified interleukin 2 had no protective effects. These data indicate that interleukin 1 protects colony formation by a pathway that is independent of interleukin 2 and that supernatants of spleen cells activated with concanavalin A probably contain significant amounts of interleukin 1. (Author abstract) (64 Refs)

38. IDENTIFICATION OF A T CELL-DERIVED B CELL GROWTH FACTOR DISTINCT FROM INTERLEUKIN 2.

Howard M, Farrar J, Hilfiker M, Johnson B, Takatsu K, Hamaoka T, Paul WE
Lab. Immunology, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
J Exp Med; 155(3):914-923 1982

Long-term culture of BALB/c mouse B lymphocytes in which induced supernatants from a T cell hybridoma (B151K12) sustain slow proliferation of lipopolysaccharide-activated B cells suggested the existence of a T cell-derived growth factor. Such a factor was identified in induced supernatants from mouse thymoma EL4 by gel filtration analysis. The B cell growth factor is distinct from interleukin 2. It co-stimulates with anti-IgM antibodies in short term cultures of purified B lymphocytes to produce polyclonal B cell proliferation but not antibody-forming cell production. The factor is not mitogenic for resting B cells and interacts with anti-IgM-activated B cells in a non-H-2-restricted manner. (28 Refs)

39. THE PURIFICATION AND PROPERTIES OF HUMAN T CELL GROWTH FACTOR.

Mier JW, Gallo RC
(c/o Gallo) Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
J Immunol; 128(3):1122-1127 1982

Human T cell growth factor (TCGF) has been purified more than 800-fold from serum-free lymphocyte conditioned media by utilizing ion exchange chromatography with DEAE-Sepharose, gel filtration with Ultrogel AcA54, and preparative SDS-polyacrylamide gel electrophoresis. This mitogenic protein, which is released by T cells into the incubating media after exposure to a lectin (PHA), has a mw of 13,000 as determined by SDS-PAGE and 20,000 to 25,000 on gel filtration and has an isoelectric point of 6.8. The material extracted from acrylamide gels is a single band (or 2 nearly superimposed bands) when rerun on analytical SDS gels. Partially purified material is unstable even at-70 C and requires the addition of bovine serum albumin or polyethylene glycol to maintain biologic activity. It is sensitive to proteolytic digestion but resistant to nucleases and thiol-reducing agents such as dithiothreitol. Human TCGF can be reversibly denatured with urea or SDS. Material extracted from acrylamide gels has been shown to sustain T lymphoblasts in tissue culture. In contrast to lectins, certain antigens, and crude lymphocyte conditioned media, purified TCGF does not initiate lymphocyte blastogenesis but is a highly selective mitogen for T cells previously activated by exposure to lectins or antigens. (Author abstract) (29 Refs)

40. CHARACTERIZATION OF A MACROPHAGE CHEMOKINETIC FACTOR IN TUMOR CELL CULTURE MEDIA.

Lane RD, Kaplan AM, Sondgrass MJ, Szakal AK
Dept. Anatomy, Medical Coll. Ohio at Toledo, C.S. Number 10008, Toledo, OH, 43699
J Reticuloendothel Soc; 31(2):171-184 1982

Media conditioned by tumor cells were studied for the presence of factor(s) that increase the rate of random migration (chemokinesis) of Corynebacterium parvum-activated macrophages. A capillary tube assay was developed and utilized to expediently monitor the chemokinetic activity of macrophages incubated in whole and fractionated media. Media conditioned by six different syngeneic and allogeneic mouse tumor cell lines demonstrated significantly higher chemokinetic activity than unconditioned or normal fibroblast conditioned media. The chemokinetically active component of the Lewis Lung conditioned media was found to be a trypsin sensitive, heat stable, high molecular weight (300,000-480,000 dalton range) factor that had no chemotactic (directional migration) activity. Pyran-activated macrophages also responded chemokinetically to the Lewis Lung factor while oyster glycogen and thioglycolate-elicited macrophages did not. The similarity and differences between the physical properties of the chemokinetic factor, other migration stimulating factors, and tumor-associated proteins are discussed. (Author abstract) (30 Refs)

THYMIC HORMONES AND OTHER IMMUNORESTORATIVE AGENTS

41. STUDIES OF THYMOPOIETIN PENTAPEPTIDE (TP5) ON EXPERIMENTAL TUMORS. 1. TP5 RELIEVES IMMUNOSUPPRESSION IN TUMOR-BEARING MICE.

Lau CY, Wang EY, Goldstein G
Immunopharmacology, Ortho Pharmaceutical (Canada) Ltd., Don Mills, Ontario, M3C 1L9, Canada
Cell Immunol; 66(2):217-232 1982

The allogeneic and syngeneic immune responses of tumor-bearing mice (C57BL/6 mice bearing 3LL and DBA mice bearing P815) were evaluated by the cytotoxic lymphocyte precursor unit and MLC. In general, tumor-bearing mice showed slightly enhanced immune responses 4 days after tumor inoculation. This enhanced immune response rapidly declined and about 7-10 days after tumor inoculation, both allogeneic and syngeneic responses were markedly lower than normal. Mice treated with TP5, starting 2 wk before tumor inoculation, retained normal or enhanced allogeneic and syngeneic responses up to 3 wk after tumor inoculation. When this tumor-induced suppressive effect was studied in cell transfer experiments, spleen cells from tumor-bearing mice enhanced the growth of tumors in syngeneic recipients whereas spleen cells from TP5-treated mice inhibited the growth of tumors in syngeneic recipients. Moreover, the spleen cells from TP5-treated mice also showed enhanced cytotoxic activity against tumor cells in vitro. These findings suggest that the tumors, after a transient stimulatory phase, induced immune suppressive mechanisms in the hosts' immune defenses. Treatment with TP5 prevented the development of these immune suppressive effects and spleen cells from TP5-treated tumor-bearing mice inhibited tumor growth in freshly tumor-inoculated recipients. (Author abstract) (23 Refs)

42. STUDIES ON THE MECHANISMS OF THE INHIBITORY EFFECTS OF SERUM THYMIC FACTOR ON MURINE ALLOGRAFT IMMUNITY.

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Cell Immunol; 66(2):360-371 1982

The mechanisms of the inhibitory effect of the serum thymic factor (FTS) on allograft immunity have been studied on both cellular and humoral immune responses of skin allografted mice. FTS-induced suppression of allogeneic skin graft rejection was correlated with a transient diminution of in vivo alloreactive CTL production in the spleen, whereas the generation of allo-anti-H-2 antibodies was not affected. The involvement of suppressor cells in the effect of FTS was supported by the observation that irradiated spleen cells from FTS-treated recipients (bearing a 9-day allograft) suppressed the in vitro CTL generation. (Author abstract) (29 Refs)

43. GENERATION OF A MONOCLONAL ANTIBODY AGAINST FACTEUR THYMIQUE SERIQUE (FTS).

Ohga K, Incefy GS, Wang CY, Good RA

Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Clin Exp Immunol; 47(3):725-734 1982

A monoclonal antibody against one of the thymic hormones, facteur thymique serique (FTS), was generated by hybridization between mouse NS-1 myeloma cells and BALB/c splenocytes, the latter obtained from BALB/c mice immunized with synthetic FTS coupled to mouse IgG. Enzyme-linked immunosorbent assay (ELISA) was developed and employed to detect the hybridoma secreting specific antibody. The monoclonal antibody (MA-FTS) was highly specific for FTS and did not cross-react with other thymic hormones or other unrelated peptides. MA-FTS could recognize FTS (or FTS-like molecule) in human serum and could absorb completely the FTS-like activity from human serum. (Author abstract) (25 Refs)

ACTIVE SPECIFIC IMMUNIZATION

44. IMMUNOTHERAPEUTIC EFFECTS OF TUMOR-SPECIFIC TRANSPLANTATION ANTIGENS RELEASED BY 1-BUTANOL.

Kahan BD, Pellis NR, LeGrue SJ, Tanaka T

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Cancer; 49(6):1168-1173 1982

Active immunotherapy with materials extracted from a murine methylcholanthrene-induced sarcoma using single phase solutions of 2.5% 1-butanol evoked host resistance against supralethal burdens of neoplastic cells deposited subcutaneously or delivered hematogenously. After curative resection of progressing 1 cm tumors, postsurgical immunity against subsequent subcutaneous neoplastic challenges was potentiated by weekly injections of crude butanol extracts. In a conventional therapy model, hosts bearing progressing 4 mm subcutaneous tumors displayed neoplastic regression following chemoimmunotherapy with cyclophosphamide and tumor extracts. Therapeutic effects were demonstrated not only against subcutaneous neoplasms, but also against hematogenously disseminated pulmonary and extrapulmonary metastases introduced by intravenous inoculation of sarcoma cells. These findings suggest that tumor extracts may afford potent therapeutic adjuvant for patients bearing a small body tumor burden but at high risk of disease recurrence. (Author abstract) (21 Refs)

ADOPTIVE IMMUNIZATION AND RELATED APPROACHES

45. IMMUNOTHERAPY OF A CHEMICALLY-INDUCED SARCOMA IN RATS: CHARACTERIZATION OF THE EFFECTOR T CELL SUBSET AND NATURE OF SUPPRESSION.

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J Immunol; 128(3):1112-1117 1982

Chemically-induced sarcomas (BC5), established sc and growing progressively in BN rats, were completely eliminated by iv infusion of syngeneic effector cells. The effector cells were generated from BN spleen cells immune to BC5 in a mixed lymphocyte-tumor cell culture (MLTC). Generation of a high yield of effector cells that were efficacious in eliminating BC5 in vivo necessitated: depletion of macrophages from immune spleen populations, before preparation of MLTC; addition back to MLTC of a small number of macrophages from normal spleens to attain a level of 0.5% of the spleen cells in culture; and addition of T cell growth factor on Day 5 of MLTC. With these conditions a subset of T cells was expanded. They were blast cells with surface markers W3/25 and Ia, which exhibited no cytotoxic activity in vitro, and probably functioned as a helper or amplifier element in the tumor-bearing host. Effector cells generated in MLTC with BC5, treated with mitomycin C, were specific for BC5 in vivo and did not affect growth of a viral-induced BN tumor. (Author abstract) (58 Refs)

46. LYSIS OF FRESH HUMAN SOLID TUMORS BY AUTOLOGOUS LYMPHOCYTES ACTIVATED IN VITRO WITH LECTINS.

Mazumder A, Grimm EA, Zhang HZ, Rosenberg SA

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Cancer Res; 42(3):913-918 1982

Human peripheral blood lymphocytes (PBL), obtained from patients with a variety of cancers, were incubated in vitro with phytohemagglutinin, concanavalin A, and crude or lectin-free T-cell growth factors. The lectin-activated PBL of nine patients were capable of lysing fresh autologous tumor during a 4-hr 51Cr release assay. Multiple metastases from the same patient were equivalently lysed by these activated autologous PBL. No lysis of fresh PBL or lectin-induced lymphoblast cell targets was seen, although tumor, PBL, and lymphoblast cells were shown to be equally lysable using allosensitized cells. The activated cells could be expanded without loss of cytotoxicity in crude or lectin-free T-cell growth factors. The generation of cells lytic to fresh autologous tumor was dependent on the presence of adherent cells, although the lytic cell itself was not adherent. Proliferation was not involved in the induction of lytic cells since equal lysis was induced in irradiated and nonirradiated lymphocytes. Lectin was not required in the lytic assay, and the addition of alpha-methyl-D-mannoside to concanavalin A-activated lymphoid cells did not decrease the lysis of fresh tumor cells. Activation by lectin for 3 days appears to be an efficient and convenient method for generating human cells lytic to fresh autologous tumor. These lytic cells may be of value for studies of the cell-mediated lysis of human tumor and possibly for tumor immunotherapy as well. (Author abstract) (29 Refs)

47. HUMAN TUMOUR ANTIGENS DEFINED BY CYTOTOXICITY AND PROLIFERATIVE RESPONSES OF CULTURED LYMPHOID CELLS.

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Nature; 296(5855):359-361 1982

Methods of initiating continued lymphocyte cultures (CLC) having specific antitumor reactivity are described. Blood lymphocytes were obtained from cancer patients on the morning of surgery. The lymphocytes were grown in optimal quantities of different conditioned media containing interleukin-2 (IL-2) reactivity. The resulting cultured cells were tested for cytotoxicity against a range of target cells, including freshly isolated autologous and allogeneic tumor cells. The possible presence of natural killer (NK) cells was investigated with CLC against K562 cells. CLC showed cytotoxicity against both autologous and allogeneic tumor targets, and high levels of cytotoxicity against K562 cells were found in some conditioned media. No evidence of selective reactivity against the autologous tumor alone was found. Often, cytotoxicity against allogeneic tumors of unrelated types exceeded that against autologous tumors. Use of positive mixed lymphocyte-tumor cultures (MLTC) was critical to the experiments; cultures could be initiated from MLTC-negative individuals, but no specific reactivity was found in these CLC. Isolation of blast cells was necessary; without isolation, the cultured cells showed features of polyclonal T-cell activation and high NK activity. With the MLTC-CLC, selective lysis of autologous tumors and restimulation in primed lymphocyte test assays were demonstrated. (21 Refs)

48. LONG-TERM CULTURE, CLONING, AND SURFACE MARKERS OF MIXED LEUKOCYTE CULTURE-DERIVED HUMAN T LYMPHOCYTES WITH NATURAL KILLER-LIKE CYTOTOXICITY.

Pawelec GP, Hadam MR, Ziegler A, Lohmeyer J, Rehbein A, Kumbier I, Wernet P
Immunology Lab., Medizinische Klinik, 7400 Tubingen, W. Germany
J Immunol; 128(4):1892-1896 1982

Human lymphocytes alloactivated in mixed leukocyte cultures (MLC) can exert specific cell-mediated cytotoxicity against normal allogeneic targets and against certain cell lines. The former is directed by defined alloantigens expressed by almost all normal tissues, the latter against as yet undefined structures expressed predominantly by transformed tumor and virus-infected cells. This type of alloantigen-unrestricted cytotoxicity may be considered analogous to the spontaneous cytotoxicity mediated by unprimed, freshly isolated normal lymphocytes designed 'natural killing' (NK). The NK-like cytotoxic cells recovered from MLC are shown here to be susceptible to the growth-promoting properties of interleukin 2 (IL 2) containing culture supernatants of phytohemagglutinin-stimulated leukocytes. The NK-like cytotoxic patterns are retained for the finite (65 to greater than 80 days) life spans of these IL 2-dependent cell lines. From these, clones can be isolated by limiting dilution, which manifest exclusively NK-like or alloantigen-directed cytotoxicity. The cloned cells also retain cytotoxic activity up to the end of their life spans. Surface marker phenotyping of selected clones shows that they are mature activated T cells (OKT3+, Lyt-3+, UCHT1+, HLA-DR+, HTA1-). Cloned cells can possess either of the mutually exclusive OKT4+ /OKT8-or OKT4-/OKT8+ phenotypes, but with no relation to cytotoxic or helper functions. Two monoclonal antibodies, OKM1 and M522, which are known to deplete almost all NK activity from freshly prepared peripheral blood mononuclear cells, react differently on cloned cells M522 is expressed only by clones with cytotoxic function (NK-like or alloantigen-directed), whereas OKM1 is expressed only weakly on NK-like clones. In contrast, expression of structures detected by the rat monoclonal antibody YD1/48.HLK is restricted exclusively to those clones with NK-like function. The results presented here indicate that human NK-like phenomena are amenable to analysis at the clonal level by using IL 2-driven cell lines. (Author abstract) (34 Refs)

49. TWO DISTINCT HUMAN CLONED T CELL LINES THAT EXHIBIT NATURAL KILLER-LIKE AND ANTI-HUMAN EFFECTOR ACTIVITIES.

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J Immunol; 128(4):1749-1752 1982

Cloned T cell lines from mixed lymphocyte cultures stimulated with autologous Epstein Barr virus- (EBV) transformed lymphoblastoid cell line (LCL) cells were established using a limiting dilution technique in the presence of T cell growth factor (TCGF). The T cell lines included two distinct clones of cytotoxicity T cells (Tc) in addition to EBV-specific Tc. A cytotoxic profile of one cloned line was similar to that of endogenous NK cells in peripheral blood. The other cloned Tc line showed an anti-human cytotoxicity. The susceptible targets for this latter Tc line were various human cells, including autologous LCL and peripheral blood lymphocytes (PBL), stimulated with pokeweed mitogen, along with NK-sensitive and NK-resistant cell lines. Weak cytotoxic activity was detected against various xenogeneic cell lines. Furthermore, autologous and allogeneic cloned T cell lines were resistant to killing by the anti-human effector clone. These two distinct cloned Tc lines expressed the Leu-1 and Leu-2a antigens, which are markers of suppressor/cytotoxic T cells. (Author abstract) (23 Refs)

SEROTHERAPY AND RELATED APPROACHES

50. USE OF ANTI-T-CELL MONOCLONAL ANTIBODY OKT3 TO PREVENT ACUTE GRAFT-VERSUS-HOST DISEASE IN ALLOGENEIC BONE-MARROW TRANSPLANTATION FOR ACUTE LEUKAEMIA.

Prentice HG, Janossy G, Skeggs D, Blacklock HA, Bradstock KF, Goldstein G, Hoffbrand AV
Academic Dept. Haematology, Royal Free Hosp. Sch. Medicine, London, England
Lancet; 1(8274):700-703 1982

Seventeen patients who received allogeneic bone-marrow transplants from matched or slightly mismatched (in 4 patients) siblings were observed for at least 60 days or until acute graft-vs-host disease (GvHD) developed. All donor marrows after preliminary manipulation were incubated with 1 mg of the murine monoclonal antibody OKT3 before infusion in an attempt to deplete them of immunocompetent T lymphocy tes (opsonization). In 3 of the 17 patients acute GvHD of Grade II or greater developed. Two of these patients died, but they had disseminated cytomegalovirus infection as well as GvHD. Eleven patients showed no evidence of acute GvHD, and 4 had transient limited skin rashes (Grade I GvHD). Opsonization of T Lymphocytes has reduced the incidence of severe acute GvHD in this unit from 79% in an earlier group of 14 patients to 18% when added to prophylactic methotrexate. (Author abstract) (33 Refs)

51. TREATMENT OF B-CELL LYMPHOMA WITH MONOCLONAL ANTI-IDIOTYPE ANTIBODY.

Miller RA, Maloney DG, Warnke R, Levy R
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N Engl J Med; 306(9):517-522 1982

A 67-yr-old man with nodular, poorly differentiated, lymphocytic malignant lymphoma was treated with monoclonal anti-idiotype antibody. Partial responses were produced with leukocyte interferon and chemotherapy (cyclophosphamide, vincristine, and prednisone). Progressive lymphoma refractive to chemotherapy was shown by biopsy to be diffuse, poorly differentiated lymphocytic lymphoma. Anti-idiotype antibody (4D6) was given in a continuous 6-hr infusion. Plasmapheresis did not reduce the idiotype level. With 15 mg anti-idiotype antibody, a dramatic decrease in the idiotype level was noted. No toxicity or side effects were observed. Doses of 40 and 75 mg caused progressively greater decreases in serum idiotype; after 150 mg idiotype levels remained undetectable. The detectability of anti-idiotype coincided with the disappearance of serum idiotype. No measurable tumor response was noted after five doses of anti-idiotype; however, anti-idiotype penetrated and bound to cells within the lymph node. The patient's condition improved following four injections of 4D6, measurable tumor response occurred after the 75-mg dose, and over the next 3 wk the patient's enlarged lymph nodes gradually became smaller. The liver and spleen returned to normal size, tumors on the scalp disappeared, and platelet count and Hb rose to normal levels. Treatment was discontinued after a total of eight doses of antibody over 4 wk. The patient has remained in remission without further therapy for greater than 6 mo. (20 Refs)

52. STUDIES ON THE ABILITY OF MONOCLONAL ANTIBODIES TO SELECTIVELY MEDIATE COMPLEMENT-DEPENDENT CYTOTOXICITY OF HUMAN MYELOGENOUS LEUKEMIA BLAST CELLS.

Ball ED, Kadushin JM, Schacter B, Fanger MW
Dept. Microbiology, Dartmouth Medical Sch., Hanover, NH, 03755
J Immunol; 128(3):1476-1481 1982

A panel of monoclonal antibodies that bind to leukemic blast cells from patients with acute myelocytic leukemia and chronic myelocytic leukemia in blast crisis was studied for their ability to mediate complement-dependent lysis of a variety of cell populations from patients with leukemia, normal blood cells, and human leukemia cell lines. Several of these monoclonal antibodies were selectively cytotoxic to myeloid leukemia cells (AML-1-99, AML-1-211, AML-2-30, CML-75, CML-115, and CML-150). Although they were all capable of binding to normal cell populations, none of these hybridomas were cytotoxic to normal cells. Three of these antibodies (AML-1-211, CML-75, and CML-150) were cytotoxic to some leukemia cell samples only after dilution of the hybridoma supernatant, ie, they showed a prozone. Binding of these three antibodies as well as another, AML-1-201, as determined in a radioimmunoassay, also showed a prozone. Other monoclonal antibodies are described (AML-2-23 and AML-2-9) that mediate complement-dependent cytotoxicity to myeloid leukemia cells as well as selected normal cell types (monocytes and lymphocytes, respectively). The potential clinical utility of these monoclonal antibodies is considered in the context of recently encountered problems in the use of monoclonal antibodies to mediate leukemia cell lysis in vivo. (Author abstract) (23 Refs)

53. MONOCLONAL ANTIBODY AGAINST A MEMBRANE ANTIGEN CHARACTERIZING LEUKEMIC HUMAN B-LYMPHOCYTES.

Forster HK, Gudat FG, Girard MF, Albrecht R, Schmidt J, Ludwig C, Obrecht JP
Pharma Res. Div., F. Hoffmann-La Roche and Co., Ltd., Basel, Switzerland
Cancer Res; 42(5):1927-1934 1982

In the diagnosis of non-Hodgkin's lymphomas, the ready characterization of the neoplastic cell lineage by analysis of cell surface markers is of great importance. We present evidence for the existence of a human B-leukemia-associated antigen recognized by a complement-fixing monoclonal antibody (anti-Y 29/55). A hybridoma was produced by fusing mouse myeloma cells and splenocytes of a mouse immunized against lymphoid cells of a patient with B-cell chronic lymphocytic leukemia. Characterization of anti-Y 29/55-reactive normal and malignant leukocytes was demonstrated by cytolysis and indirect immunofluorescence. This revealed reactivity with an antigen on B lymphoma cells (11 patients), on leukemic lymphocytes in B-cell chronic lymphocytic leukemia (13 patients), and on malignant cells in hairy-cell leukemia (2 patients) but not on leukemic cells of T-cell acute lymphoblastic leukemia (1 patient), on T-lymphoma cells (1 patient), on cells of acute myeloblastic leukemia (4 patients), or of chronic myeloid leukemia (4 patients). No specific cytolysis occurred with B- and T-peripheral blood lymphocytes from (a) healthy donors (16 individuals), (b) patient with reactive lymphocytosis (1 patient), (c) nonleukemic multiple myeloma (6 patients), or (d) Hodgkin's disease (3 patients). Surface immunoglobulin-positive, sheep RBC-negative lymphocytes isolated from human spleen (3 individuals), tonsils (7 individuals), and lymph nodes (1 individual), however, we recognized. It is concluded that leukemic B-cells carry a marker characteristic of nonrecirculating sessile B-lymphocytes. (Author abstract) (54 Refs)

54. EFFECT OF A MONOCLONAL ANTI-LARGE GRANULAR LYMPHOCYTE ANTIBODY ON THE HUMAN NK ACTIVITY.

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J Immunol; 128(3):1097-1101 1982

A monoclonal hybridoma antibody of IgGIa subclass was produced by fusing NS-1 myeloma cells with spleen cells of a mouse immunized with human LGL cells. This hybridoma antibody, termed NK-8, was reactive by indirect immunofluorescence with 33% of peripheral blood LGL cells and 70% of LGL forming conjugates with K-562 cells. Monocytes, granulocytes, and other lymphocytes were nonreactive. In iodinated protein A binding assays NK-8 was nonreactive with all kinds of leukemia and lymphoma lines tested and showed activity only against LGL cells. NK-8 inhibited the LGL-mediated cytotoxicity against K-562 cells by 50 to 60% without complement and inhibited the K-562 induced interferon production from the LGL population. However, the spontaneous cytotoxicity against human skin fibroblasts was augmented if the effector cells were pretreated with NK-8. (Author abstract) (17 Refs)

55. BIOSYNTHESIS AND PROCESSING OF A HUMAN T LYMPHOCYTE ANTIGEN.

Bergman Y, Levy R
Howard Hughes Medical Inst., Stanford Univ., Stanford, CA, 94305
J Immunol; 128(3):1334-1340 1982

The biosynthesis and processing of Leu-1, a human T lymphocyte antigen, has been studied with the use of a monoclonal antibody. This molecule exists on the cell surface as a 67,000 mw glycoprotein. Through a series of pulse-labeling studies, in conjunction with the use of the antibiotic tunicamycin and the enzyme Endo-H, the details of glycosylation, processing, and deposition at the cell membrane were examined. The protein backbone of the molecule is 58,000 mw. High-mannose sugars are added to asparagine residues during synthesis. Within 20 min, these high mannose sugars are converted to complex type carbohydrates, including fucose. The fully processed glycoprotein appears at the cell surface within 30 min after synthesis. This sequence of events is similar to that for other cell surface glycoproteins, including HLA and vesicular stomatitis virus glycoprotein. (Author abstract) (35 Refs)

56. PRODUCTION OF MONOCLONAL ANTIBODY ALPHAPRO3 RECOGNIZING A HUMAN PROSTATIC CARCINOMA ANTIGEN.

Ware JL, Paulson DF, Parks SF, Webb KS
Dept. Surgery, Div. Urology, Duke Univ. Medical Center, Durham, NC, 27710
Cancer Res; 42(4):1215-1222 1982

The monoclonal antibody alphaPro3 recognizes an antigen concentrated in human primary prostatic carcinoma tissue removed surgically. Although the antigen was detectable in extracts of hu man normal and malignant nonprostatic tissue, as well as in benign prostate tissue, quantitative absorption analysis revealed a substantially greater quantity of the antigen in malignant prostate tissue. The antigen recognized by alphaPro3 in primary prostatic carcinoma has an apparent nonreduced molecular weight of 175,000 and an apparent subunit molecular weight of 54,000. This antigen, p54, appears to be present on the surface of cultured prostatic tumor cells of the PC-3 cell line, but its location in vivo has been defined. Successful competition between alphaPro3 and prostatic carcinoma patient serum immunoglobulin for a Mr 54,000 antigen (reduced molecular weight) present in prostatic carcinoma tissue extract suggests that p54 may play a significant role in the immunobiology of prostatic carcinoma. AlphaPro3 has potential as a sensitive probe for an antigen relevant to human tumor biology. (Author abstract) (46 Refs)

57. INHIBITION OF MURINE T CELL-MEDIATED CYTOLYSIS AND T CELL PROLIFERATION BY A RAT MONOCLONAL ANTIBODY IMMUNOPRECIPITATING TWO LYMPHOID CELL SURFACE POLYPEPTIDES OF 94,000 AND 180,000 MOLECULAR WEIGHT.

Pierres M, Goridis C, Golstein P
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Eur J Immunol; 12(1):60-69 1982

The monoclonal antibody methodology was used to identify membrane structures involved in T cell functions. To optimize chances to produce and detect relevant antibodies, a xenogeneic sensitization protocol was utilized and hybridoma supernatants were screened, on functional rather than structural grounds, for their ability to inhibit a given function. The test function was T cell-mediated cytolysis. Mouse cytolytic anti-allogeneic cell populations were used to sensitize a rat, the spleen cells of which were fused to produce hybridomas; the supernatants of the latter were screened for their ability to inhibit mouse T cell-mediated cytolysis in vitro. Several inhibitory antibodies were obtained, one of which, H35-89.9 monoclonal antibody, was studied in more detail. It inhibited specific and concanavalin A (Con A)-mediated cytolysis by T cells, by acting on the effector cells. it reversibly inhibited soluble antigen-, alloantigen and Con A-induced T cell proliferation (but not LPS-induced B cell proliferation), after the production of interleukin 2, by acting on the responder cells. It also had a desagglutinating effect on Con A and LPS blasts and on EL4 cells. It immunoprecipitated from thymocyte membrane preparations two structures of 94,000 and 180,000 apparent molecular wt, and recognized cell surface determinants on both T and B lymphocytes. Our findings suggest that several antibodies directed against distinct effector cell membrane structures inhibit cytolysis. The case of H35-89.9 monoclonal antibody, which exerts multiple functional effects and immun oprecipitates two membrane polypeptides, raises the problem of the various possible relationships between these structures and functions. (Author abstract) (48 Refs)

58. HUMAN MELANOMA-ASSOCIATED ANTIGEN P97 IS STRUCTURALLY AND FUNCTIONALLY RELATED TO TRANSFERRIN.

Brown JP, Hewick RM, Hellstrom I, Hellstrom KE, Doolittle RF, Dreyer WJ
Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Nature; 296(5853):171-173 1982

Cell surface glycoprotein p97 (mol wt 97,000), in SK-MEL 28 melanoma cells, was purified by affinity chromatography with monoclonal antibody, followed by sodium dodecyl-polyacrylamide gel electrophoresis. The N-terminal acid sequence was determined with the use of a new, highly sensitive protein sequencer. Amino acid sequence analysis of purified p97 yielded a sequence of 12 residues at the N-terminus. Computer search of the Newat amino acid sequence library showed this sequence was homologous to the N-terminal sequence of transferrin: 7 of the 12 residues were identical. This homology is considered significant for two reasons: first, the two least common amino acid residues, Trp and Cys, are among those conserved, and second, six of the seven conserved residues are also conserved at the N-terminus of lactotransferrin. This homology was confirmed by the observation that antiserum to denatured p97 cross-reacted with denatured transferrin and lactotransferrin. p97 was also functionally related to transferrin and lactoferrin in that it binds iron. The presence of p97 on certain cell types suggests that its function may be translocation of iron. (15 Refs)

59. A CELL-SURFACE ANTIGEN WHICH IS PRESENT IN THE GANGLIOSIDE FRACTION AND SHARED BY HUMAN MELANOMAS.

Yeh MY, Hellstrom I, Abe K, Hakomori S, Hellstrom KE
(c/o Hellstrom, I.) Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Int J Cancer; 29(3):269-275 1982

We have raised a hybridoma, 4.2, which forms an IgM antibody to an antigen expressed on cultivated cells from most human melanomas, more infrequently on cells from other human tumors, and very weakly on cultivated fibroblasts, T cells and B cells. The antigen can be detected in biopsy material of human melanoma and, in smaller amounts, in fresh samples of normal human lung and kidney. Preliminary biochemical characterization indicates that it is associated with the ganglioside fraction. We feel that the antigen (referred to as 4.2) has a sufficient degree of tumor specificity to be rated as a human melanoma-associated antigen. (Author abstract) (24 Refs)

60. UNIQUE GLYCOPROTEIN-PROTEOGLYCAN COMPLEX DEFINED BY MONOCLONAL ANTIBODY ON HUMAN MELANOMA CELLS.

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Proc Natl Acad Sci USA; 79(4,part1):1245-1249 1982

A monoclonal antibody, 9.2.27, with a high specificity for human melanoma cell surfaces has been utilized for biosynthetic studies in M21 human melanoma cells to define a unique antigenic complex consisting of a 250-kilodalton N-linked glycoprotein and a high mol wt proteoglycan component larger than 400 kilodaltons. The 250-kilodalton glycoprotein has endoglycosidase H-sensitive precursors and shows a lower apparent mol wt after treatment with neuraminidase. The biosynthesis of the proteoglycan component is inhibited by exposure of M21 cells to the monovalent ionophore monensin; this component can be labeled biosynthetically with 35SO4, is sensitive to beta-elimination in dilute base, and is degraded by both chondroitinase AC and ABC lyases, suggesting that it is a chondroitin sulfate proteoglycan. These data demonstrate that the antigenic determinant recognized by monoclonal antibody 9.2.27 is located on a glycoprotein-proteoglycan complex which may have unique implications for the interaction of glycoconjugates at the human melanoma tumor cell surface. (Author abstract) (29 Refs)

61. GENETIC CHARACTERIZATION OF A POLYMORPHIC MURINE CELL-SURFACE GLYCOPROTEIN.

Lesley J, Trowbridge IS
Dept. Cancer Biology, Salk Inst., Post Office Box 85800, San Diego, CA, 92138
Immunogenetics; 15(3):313-320 1982

As described in the preceding paper, monoclonal antibodies have been raised by immunization of rats with mouse hematopoietic cells which detect a major cell-surface glycoprotein (Mr = 95,000) of mouse bone-marrow cells of the granulocytic series. While most of the monoclonal antibodies detect this molecule on bone-marrow and spleen cells of all mouse strains, two antibodies recognize alternative allelic forms of the molecule. One alloantigen is expressed in all the remaining inbred strains examined. The alloantigens are codominantly expressed on the cells of F1 mice. Backcrosses of DBA/2 and C57BL/6 with F1 mice (B6D2F1) confirmed that a single genetic locus is involved in the expression of the two antigenic forms and demonstrated linkage to Ly-m11 which has previously been mapped to mouse chromosome 2. These genetic mapping experiments and the biochemical properties of the glycoprotein suggested that it might be identical to a glycoprotein first identified on murine fibroblasts by Hughes and August and designated Pgp-1. This has been firmly established by exchange of monoclonal antibody reagents and sequential immunoprecipitations. (Author abstract) (16 Refs)

62. BIOCHEMICAL CHARACTERIZATION AND CELLULAR DISTRIBUTION OF A POLYMORPHIC, MURINE CELL-SURFACE GLYCOPROTEIN EXPRESSED ON LYMPHOID TISSUES.

Trowbridge IS, Lesley J, Schulte R, Hyman R, Trotter J
Dept. Cancer Biology, Salk Inst., Post Office Box 85800, San Diego, CA, 92138
Immunogenetics; 15(3):299-312 1982

A murine leukocyte surface glycoprotein (Mr = 95,000) has been defined by means of xenogeneic monoclonal antibodies. In normal hematopoietic tissues, the glycoprotein is found in highest amounts in the bone marrow. Flow cytometric analysis shows that essentially all bone-marrow cells express the glycoprotein and that it is a major component of a subpopulation of cells containing predominantly granulocytic precursors. In contrast, only about 5% of thymocytes express sufficient glycoprotein to be detected by flow cytometric analysis, although under stringent conditions up to 20% of thymocytes are susceptible to complement-mediated cytotoxicity using a monoclonal antibody against the glycoprotein. Functional assays showed that both prothymocytes and colony forming unit-spleen express the glycoprotein which is broadly distributed on murine hematopoietic tumor cell lines. However, although some Thy-1+ (T) cell lymphomas express large amounts of the glycoprotein, others do not express detectable quantities of the molecule. The glycoprotein is not restricted to hematopoietic cells and can be detected on lung, kidney, brain, and liver as well as cultured fibroblasts. Monoclonal antibodies against the glycoprotein cross-react with an antigen present on human cells. As described in the accompanying paper, the glycoprotein exists in two antithetical allelic forms and we show that it is identical to a polymorphic surface molecule independently characterized by Colombatti and co-workers. (Author abstract) (41 Refs)

63. MONOCLONAL ANTIBODY TO TRANSFERRIN RECEPTOR BLOCKS TRANSFERRIN BINDING AND INHIBITS HUMAN TUMOR CELL GROWTH IN VITRO.

Trowbridge IS, Lopez F
Dept. Cancer Biology, Salk Inst. Biological Studies, P. O. Box 85800, San Diego, CA, 92138
Proc Natl Acad Sci USA; 79(4,part1):1175-1179 1982

A murine hybridoma has been obtained that produces a monoclonal antibody against the human transferrin receptor. In contrast to previously characterized monoclonal antibodies that recognize the transferrin receptor, this antibody, designated 42/6, blocks the binding of transferrin to its receptor and inhibits the growth of the human T leukemic cell line, CCRF-CEM, in vitro. Inhibition of cell growth was dose dependent, and as little as 2.5 ug of purified antibody per ml had a detectable effect, even though transferrin was present in the tissue culture medium in large molar excess. Cells grown in the presence of antibody for 7 days accumulated in S phase of the cell cycle. The addition of iron to antibody-treated cultures in the form of ferric complexes or ferrous sulfate did not overcome the growth inhibitory effects of the anti-transferrin-receptor antibodies. This result suggests that either transferrin is the only means by which CCRF-CEM leukemic cells can be provided with sufficient iron in vitro or that ot her factors in addition to iron starvation are involved in the antibody-mediated growth inhibition. The inhibition of cell growth by 42/6 monoclonal antibody suggests that monoclonal antibodies against proliferation-associated cell surface antigens, such as the transferrin receptor, may be useful pharmacological reagents to modify cell growth in vitro. (Author abstract) (46 Refs)

64. A SINGLE MONOCLONAL ANTI-IA ANTIBODY INHIBITS ANTIGEN-SPECIFIC T CELL PROLIFERATION CONTROLLED BY DISTINCT IR GENES MAPPING IN DIFFERENT H-2 I SUBREGIONS.

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Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Immunol; 128(3):1409-1413 1982

A xenogeneic rat anti-mouse Ia monoclonal antibody, M5/114 (gamma2b,kappa) was studied for its effects in vitro on T cell proliferative responses. Strain distribution studies revealed that M5/114 could inhibit I-A subregion-restricted T cell responses of the H-2b,d,q,u but not the H-2f,k,s haplotypes, indicating that this xenoantibody recognizes a polymorphic determinant on mouse Ia molecules. This same monoclonal antibody was found to inhibit BALB/c(H-2d) T cell proliferation to both G60A30T10 and G58L38phi4. The Ir genes regulating responses to these antigens map to either the I-A subregion (GAT), or the I-A and I-E subregions (GLphi), raising the possibility that M5/114 recognizes both I-A and I-E subregion-encoded Ia glycoproteins. It could be shown, using appropriate F1 responding cells, that M5/114 does in fact affect GAT and GLphi responses by interaction with both the I-A and the I-E subregion products, and not by an nonspecific effect resulting from binding to the I-A subregion product alone. These results are consistent with genetic and biochemical studies directly demonstrating that M5/114 recognizes AalphaAbeta and EalphaEbeta molecular complexes. The existence of a shared epitope on I-A and I-E subregion products suggests the possibility that these molecules arose by gene duplication. Finally, the precise correlation between the Ia molecules recognized by M5/114 and the ability of this antibody to block T cell responses under Ir gene control strengthens the hypothesis that Ia antigens are Ir gene products. (Author abstract) (33 Refs)

65. MAC-2, A NOVEL 32,000 M4 MOUSE MACROPHAGE SUBPOPULATION-SPECIFIC ANTIGEN DEFINED BY MONOCLONAL ANTIBODIES.

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J Immunol; 128(3):1221-1228 1982

Two monoclonal antibodies, M3/31 and M3/38, were obtained by fusion of mouse myeloma cells with rat spleen cells immunized to immunoadsorbent-purified macrophage glycoproteins. Co-precipitation experiments show that antigenic determinants recognized by these two antibodies reside on the same molecular species, termed Mac-2. Mac-2, an antigen of 32,000 Mr, is synthesized by and expressed on the surface of thioglycollate-elicited macrophages as shown by [35S]-methionine and 125I labeling. Saturation binding experiments show that thioglycollate-elicited macrophages express 1.7 x 10(5) Mac-2 sites/cell. Thioglycollate-elicited macrophages are strongly absorptive for 125I-labeled M3/38 MAb. Kidneys are also absorptive; however, evidence is presented pointing to the nonspecificity of this absorption. Lymph node and thymus are negative, whereas spleen and bone marrow are weakly absorptive, probably due to stromal cells. Nonlymphoid tissues, such as lung, liver, heart, and brain, exhibit slight or no absorbing capacity. Cell suspensions from spleen, bone marrow, thymus, and peripheral lymph node are greater than 99% Mac-2-by immunofluorescent flow cytometry. In contrast, thioglycollate-elicited macrophages are greater than 96% strongly positive for Mac-2. Only 20% of peptone-elicited cells are weakly positive, whereas resident peritoneal macrophages and other macrophages elicited by Listeria monocytogenes, Con A, or LPS are greater than 98% negative. SDS-PAGE of [35S]-methionine-labeled Mac-2 shows that thioglycollate-elicited macrophages synthesize 10-to 30-fold more Mac-2 than other peritoneal macrophage subpopulations, whereas all types of peritoneal macrophages synthesize and express on their surfaces similar amounts of the Mac-1 antigen. Mac-2 antigen is therefore induced in macrophages only in response to specific differentiative signals. (Author abstract) (30 Refs)

66. NEOPLASTIC B CELLS AS TARGETS FOR ANTIBODY-RICIN A CHAIN IMMUNOTOXINS.

Vitetta ES, Krolick KA, Uhr JW

Dept. Microbiology, Univ. Texas Health Science Center at Dallas, Dallas, TX, 75235

Immunol Rev; 62:159-183 1982

Studies assessing the capacity of antibody-ricin A chain conjugates (immunotoxins) to selectively kill tumor cells from the murine B cell tumor, BCL1, are reviewed. The extent to which BCL1 cells could be selectively killed in vitro was determined. The ability of BCL1 cells present in tumor-infiltrated bone marrow to kill in vitro without harming hematopoietic stem cells was examined. Experiments designed to determine the effectiveness of the anti-immunoglobulin (Ig) immunotoxins in vivo using mice bearing advanced BCL1 tumors are described. The BCL1 tumor model, preparation of antibodies, preparation of anti-Ig immunotoxins, and adoptive transfer of BCL1 cells treated with antibody A-chain immunotoxin are discussed. The implications for bone marrow transplantation in the treatment of malignancy are considered in relation to the elimination of BCL1 tumor cells from bone marrow. (56 Refs)

67. MONOCLONAL ANTIBODY-RICIN OR RICIN A CHAIN HYBRIDS: KINETIC ANALYSIS OF CELL KILLING FOR TUMOR THERAPY.

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Lab. Neurochemistry, Section on Biophysical Chemistry, Natl. Inst. Mental Health, Bethesda, MD, 20205

Immunol Rev; 62:75-91 1982

Effects of three different types of ricin hybrids (antibody thioether linked to intact ricin, antibody disulfide linked to the ricin A chain, and antibody-S-S-A chain to which the ricin B chain is added as a separate entity) conjugated with monoclonal antibody having affinity for the murine thymic adult differentiation antigen Thy 1 on targeted cells are reviewed in relation to tumor cytotoxicity. Entry mechanisms and data regarding parent toxins are considered. (30 Refs)

68. MONOCLONAL ANTIBODIES TO XENOTROPIC AND MCF MURINE LEUKEMIA VIRUSES DERIVED DURING THE GRAFT-VERSUS-HOST REACTION.

Portis JL, McAtee FJ, Cloyd MW

Dept. Health and Human Services, Public Health Service, NIH, Natl. Inst. Allergy and Infectious Diseases, Rocky Mountain Lab., Hamilton, MT, 59840

Virology; 118(1):181-190 1982

The humoral immune response during adult graft-vs-host reaction (GVHR) was assessed by the recovery of antibody-forming host spleen cells using cell fusion techniques. Two parent - F1 strain combinations were studied, (B6 x D2)F1 and (NFS x AKR)F1 injected with the respective parental spleen cells. Hybridomas derived from recipient spleens were found to produce antibody with predominant specificity for murine leukemia virus (MuLV) envelope (env) polypeptides. The recovery of anti-MuLV monoclonal antibodies was dependent on the donor strain. Thus, D2-(B6 x D2)F1 and AKR - (NFS x AKR) resulted in a high incidence of anti-MuLV antibody production among the primary fusion products whereas no anti-MuLV hybridomas were recovered when B6 or NFS, respectively, were used as donors. Hybridomas derived from D2-(B6 x D2)F1 produced anti-MuLV antibodies of two general specificities: (1) broadly reactive, detecting determinants expressed by ecotropic and xenotropic MuLV, and (2) xenotropic MuLV specific. The latter group included antibodies reacting with all xenotropic MuLV and antibodies with xenotropic MuLV strain specificity. Xenotropic MuLV-specific determinants were expressed by gp70, p15(E), and the gp70-p15(E) complex (gp90). This is, to our knowledge, the first report of monoclonal antibodies specific for xenotropic MuLV. In contrast, hybridomas derived from AKR - (NFS x AKR) produced antibodies which reacted predominantly with unique determinants of a subgroup of MCF viruses. These results suggested that the anti-MuLV antibody repertoire expressed during GVHR is influenced by the endogenous MuLV of the respective mouse strain combination. (Author abstract) (25 Refs)

CLINICAL IMMUNOLOGY

69. EFFECT OF SYSTEMIC INTERFERON ON NATURAL KILLER CELL FUNCTION IN MELANOMA PATIENTS.

Golub SH, Burk M
Univ. California Los Angeles, Los Angeles, CA
UCLA Cancer Cent Bull; 9(1):3-6 1982

The effect of human leukocyte interferon on natural killer (NK) cell function was examined in patients with disseminated malignant melanoma. Treatment of 16 patients with human leukocyte interferon was not associated with any notable change in the proportion or absolute number of major lymphocyte subpopulations, including T and B cells and Fc receptor cells. When NK activity was tested against the myeloid leukemia target K562, NK activity declined at 24 hr after the first administration of interferon. Subsequently, activity rose, with peak activity found at 7 days of continuous daily treatment. When five patients who may have had some clinical benefit from interferon treatment were compared with four patients with rapid disease progression, no difference in the degree to which NK cytotoxicity was augmented by interferon was seen. Results of cellular analysis suggested that in vivo treatment with interferon results in both an increase in cytotoxicity by mature NK cells and recruitment of additional cells from precursors of NK cells into the NK differentiation pathway. (7 Refs)

70. DEFICIENT NATURAL KILLER CELL ACTIVITY IN A PATIENT WITH FANCONI'S ANAEMIA AND SQUAMOUS CELL CARCINOMA. ASSOCIATION WITH DEFECT IN INTERFERON RELEASE.

Hersey P, Edwards A, Lewis R, Kemp A, McInnes J
Medical Res. Dept., Kanematsu Memorial Inst., Sydney Hosp., Sydney, N.S.W. 2000, Australia
Clin Exp Immunol; 48(1):205-212 1982

A child with Fanconi's anemia diagnosed at 7 yr of age presented in adult life with lymphopenia, recurrent warts and Bowen's disease. The latter resulted in the development of multiple cutaneous squamous cell carcinomas which metastasized to the skeleton. Investigation of her immune function revealed selective defects in natural killer (NK) cell activity. Humoral immunity and several tests of cell-mediated responses were within normal or became normal after treatment with levamisole or transfer factor. Analysis of the defect in NK activity revealed that low levels could be induced in vitro by fibroblast interferon. Stimulation of blood lymphocytes from the patient with the interferon inducer poly(I)-poly(C) resulted in an increase in NK activity but incubation of her lymphocytes on tumor cells did not result in an increase in NK activity or the release of interferon. This contrasted with the marked increase in NK activity and interferon release observed when lymphocytes from normal controls were incubated on tumor cells. These findings suggested the absence of NK activity in this patient was secondary to a defect in interferon release from lymphocytes on exposure to tumor antigens. It is considered that these defects may have been an important predisposing factor in the development of malignancy in this patient and possibly other patients with Fanconi's anemia. (Author abstract) (20 Refs)

71. NATURAL CYTOTOXICITY AND ANTIBODY-DEPENDENT CYTOTOXICITY IN SOLID TUMOR CANCER PATIENTS: REGULATION BY ADHERENT CELLS.

DeBoer KP, Braun DP, Harris JE
(c/o Braun) 1725 West Harrison, Suite 830, Chicago, IL, 60612
Clin Immunol Immunopathol; 23(1):133-144 1982

Natural cytotoxicity (NK) and antibody-dependent cellular cytotoxicity (ADCC) were measured in peripheral blood mononuclear cells (PBMC) from 30 normal subjects and from 60 untreated patients with solid tumors at various stages of disease. NK, but not ADCC, activity of PBMC from patients with disseminated disease was significantly lower than NK activity of either normal donors or patients with localized disease. This decreased NK activity was not related to decreased numbers of T cells or target-binding cells or to immune complex levels in patient sera. Glass-adherent cell depletion augmented decreased NK levels significantly to normal levels of function. Addition of indomethacin did not alter NK activity in any of the patients studied. We conclude that decreased NK activity in PBMC from cancer patients with disseminated disease is due to a suppression which may be mediated by glass-adherent cells. This is not dependent on a prostaglandin-mediated mechanism of suppression. (Author abstract) (28 Refs)

72. NATURAL KILLER ACTIVITY IN SPLEENS AND LYMPH NODES FROM PATIENTS WITH HODGKIN'S DISEASE.

Ruco LP, Procopio A, Uccini S, Marcorelli E, Baroni CD
IV Cattedra di Anatomia ed Istologia Patologica, Universita di Roma, Viale Regina Elena 324, 00161 Roma, Italy
Cancer Res; 42(5):2063-2068 1982

Natural killer (NK) activity against K-562 myeloid cell line was evaluated in 21 spleens and 14 lymph nodes from patients with Hodgkin's disease (HD). NK activity of eight HD-involved (HD-) spleens [556 lytic units (LU)] was found five-fold higher than that of 13 HD-uninvolved (HD-) spleens (112 LU) (p less than 0.01). Moreover, NK activity of HD+ spleens was significantly different (p less than 0.05) from that of three spleens involved by non-HD lymphoma (100 LU). NK activity of four spleens from nonneoplastic patients (250 LU) was intermediate between those of HD+ and HD- spleens. Lymph node cells were about 10-fold less cytotoxic. NK activity of seven HD+ lymph nodes (43 LU) was three-fold higher than that of three lymph nodes involved by non-HD lymphoma (8 LU). However, these differences were not statistically significant. Our data are compatible with increased NK activity in HD+ tissues as well as with depressed NK activity in HD- tissues. The observation that NK activity of peripheral blood leukocytes from nine HD patients (116 LU) (p less than 0.05 only at 100:1 effector:target cell ratio) may support the latter interpretation. Partial characterization of effector cells in HD+ and in HD- spleens indicated that, in both instances, NK cells were nonadherent and almost equally distributed between the erythrocyte-negative and -positive cell fractions. Finally, NK activity of both HD+ and HD-spleen cells could be further potentiated in vitro by interferon. (Author abstract) (30 Refs)

73. IMMUNODIAGNOSIS OF HUMAN MELANOMA: CHARACTERIZATION OF HUMAN MELANOMA ANTIGENS AND THEIR DETECTION IN SERA OF MELANOMA PATIENTS BY RADIOIMMUNOASSAY.

Ishii Y, Mavligit GM
Dept. Pathology, Sapporo Medical Coll., S1 W17, Sapporo 060, Japan
Oncology; 39(1):23-28 1982

Double antibody radioimmunoassay (RIA), using radioiodinated melanoma-associated antigens (MAA), rabbit antiserum raised against 3 M KCl extract of human melanoma (AHMS) and goat antirabbit IgG antibody, was employed for the detection of MAA in tumors as well as in sera of melanoma patients. MAA were partially purified from crude KCl extract of melanoma tissue by affinity column chromatography using AHMS and concanavalin A. A high content of MAA was detected in all but one melanoma extract, while normal tissue and nonmelanoma tumor extracts contained MAA to a much lesser extent than did melanoma extracts. MAA were also found in melanoma patients' sera (20/45) but not in sera of normal donors (0/10) and colon cancer patients (0/10). Immunochemical data suggest that AHMS-defined MAA consist of two major glycoproteins with mol wt of 37K and 31K daltons, which does not cross-react either with carcinoembryonic antigen or beta2-microglobulin or with BCG. (Author abstract) (29 Refs)

74. RELATIONSHIP BETWEEN CIRCULATING IMMUNE COMPLEXES AND URINARY ANTIGENS IN HUMAN MALIGNANCY.

Huth JF, Gupta RK, Morton DL
Div. Oncology, Dept. Surgery, Univ. California Los Angeles Sch. Medicine, Factor Building, Los Angeles, CA, 90024
Cancer; 49(6):1150-1157 1982

Urine samples obtained from patients with histologically proved melanoma and sarcoma were analyzed for the presence of tumor-associated antigens by complement fixation and enzyme immunoassay. Also, serum samples obtained during 24-hr urine collection from these patients were analyzed for circulating immune complexes by the complement consumption method and by the K562 radiometric assay. Of 36 cancer patients who were positive for urinary antigen (UA) by both assays, 28 (78%) were also positive for CIC in the two assays, 6 (17%) were positive in one of the two CIC-detection assays, and 2 (5%) were negative in both assays. Of 24 patients that were negative for CIC in both assays, 10 (42%) were also negative for UA in both assays, ie, complement fixation and enzyme immunoassay; 12 (50%) were negative by one of the two assays; and only 2 (8%) exhibited UA by both assays. This relationship was more striking for melanoma than sarcoma patients. In a melanoma patient whose samples were studied sequentially during his thermochemotherapy, the fluctuations in CIC and UA were parallel. These results suggest that excretion of tumor-associated antigen into urine is not an isolated phenomenon; rather, immune complex deposition in kidneys appears to cause glomerular damage which may allow the passage of the antigens into the urine. (Author abstract) (32 Refs)

75. AMYL NITRITE MAY ALTER T LYMPHOCYTES IN HOMOSEXUAL MEN.

Goedert JJ, Wallen WC, Mann DL, Strong DM, Neuland CY, Greene MH, Murray C, Fraumeni JF, Blattner WA
Environmental Epidemiology Branch, NCI, Landow Building - Room 4C18, Bethesda, MD, 20205
Lancet; 1(8269):412-416 1982

To evaluate the recent outbreak of Kaposi's sarcoma (KS) and opportunistic infections in homosexual men, clinical, virological, and immunological data on 2 homosexual men with KS and on 15 healthy homosexual volunteers were collected. Both KS patients had regularly used amyl nitrite or butyl nitrite (AN); they had low helper/suppressor (H/S) T lymphocyte ratios before chemotherapy and high titers of antibody against cytomegalovirus (CMV). Eight of the 15 volunteers were regular AN users; 7 of the 8 had low H/S ratios due to larger than normal numbers of OKT8-positive suppressor cells and smaller numbers of OKT4-positive helper cells. In all eight AN users the fluorescence profile obtained with monoclonal antibody 9.6 (which detects the sheep E-rosette receptor) was bimodal, indicating a subpopulation of T cells with increased receptor density. A similar pattern was observed when OKT8, the antibody which detects cytotoxic suppressor cells, was used. Two of the seven men who did not use AN had abnormal fluorescence with reagent 9.6, and one of these also had a low H/S ratio. CMV-antibody titers were persistently high in 14 of the 15 healthy men, but the titers were not related to An use or T-cell abnormalities. The data suggest that nitrites may be immunosuppressive in the setting of repeated viral antigenic stimulation and may contribute to the high frequency of KS and opportunistic infections in homosexual men. (Author abstract) (35 Refs)

REVIEWS

76. IMMUNOTHERAPY OF TUMORS.

Baldwin RW

Cancer Res. Campaign Laboratories, University Park, Nottingham NG7 2RD, England

Cancer Chemotherapy 1981- The EORTC Cancer Chemotherapy Annual 3. Pinedo HM, ed. Amsterdam, Excerpta Medica, 504 pp, 1981.

Aspects of present-day immunotherapy are reviewed and some additional basic information on interferons is presented. Areas discussed are active specific immunotherapy, natural resistance to tumors (natural killer cells, macrophages), immunomodulating agents (BCG, methanol extraction residue, cell-wall preparations, muramyl dipeptide, Corynebacterium parvum, and interferon), immunostimulating compounds, and antibody-directed cytotoxic agents. (166 Refs)

77. THE HUMAN INTERFERON SYSTEM.

Berman B, Frankfort HM

Dept. Dermatology, Mount Sinai Sch. Medicine, 1 Gustave L. Levy Place, New York, NY, 10029

Int J Dermatol; 21(1):12-18 1982

Clinical uses of interferon (IF) in dermatology are reviewed. IF inhibits both DNA- and RNA-containing viruses, as well as nonviral intracellular organisms. The immunomodulatory effects of IF on phagocytosis, histamine, prostaglandin E, antibody dependent cell-mediated cytotoxicity, natural killer lymphocytes, and mitogen activation of lymphocytes are discussed. Clinical studies of IF in cases of herpes zoster, varicella, herpes simplex, vaccinia, congenital rubella, concylomata acuminata and malignant melanoma are discussed. (85 Refs)

78. IN VITRO IMMUNIZATION AS A METHOD FOR GENERATING CYTOTOXIC CELLS POTENTIALLY USEFUL IN ADOPTIVE IMMUNOTHERAPY.

Mokyr MB, Dray S
Dept. Immunology and Microbiology, Univ. Illinois at the Medical Center, Chicago, IL, 60612
Methods Cancer Res; 19:385-417 1982

The following aspects of utilization of in vitro immunized lymphoid cells in therapy are reviewed, based on studies in several mouse systems: critical factors for the success of in vitro immunization, optimal source of responder and stimulator cells, methods to potentiate the antitumor activity of in vitro immunized cells, methods to screen in vitro immunized cells for their immunotherapeutic potential, and the advantages of using in vitro immunized lymphoid cells as an adjunct to chemotherapy. In vitro immunized lymphoid cells were therapeutically superior to in vivo immunized lymphoid cells in a number of ways. Therapy with adoptively transferred cells may be improved by growing large numbers of cytotoxic cells in vitro, and repeatedly administering these cells to help maintain large numbers of cytotoxic cells within the system. The apparent role of adoptively transferred immune cells is to extend the period of time in which the concentration of tumor cells is low, allowing the recipient to develop strong antitumor immunity to cope with the remaining tumor cells. (157 Refs)

79. CELL SURFACE GLYCOPROTEIN MARKERS FOR NEOPLASIA.

Bhavanandan VP, Davidson EA
Dept. Biological Chemistry, Milton S. Hershey Medical Center, Hershey, PA, 17033
Methods Cancer Res; 19:53-105 1982

Glycoproteins that serve as cell surface markers of neoplasia are described biochemically, in relation to viral transformation, and for various animal and human cells, and the methods employed are reviewed. The animal tumors and derived cell lines discussed include the following: neuroblastoma, melanoma, ascites, hepatoma, mammary carcinoma, lung carcinoma, and leukemias and lymphomas. Glycoprotein cell surface markers in human cells are reviewed in relation to melanoma, mammary carcinoma, lung carcinoma, colon carcinoma, ovarian carcinoma, and neuroblastoma. Metabolic labeling, isolation, purification, mapping, and structural analysis techniques applied to glycoproteins are reviewed. Future studies in this field will probably take advantage of improved methods such as isoelectric focusing gels, lectin affinity chromatography, and monoclonal antibodies. Ultimately the metabolic and genetic origin of each macromolecule must be determined. In the meantime, glycoprotein cell surface marker studies may be expected to contribute to diagnostic and immunologic approaches to management of disease. (313 Refs)

80. CELL SURFACE MARKERS IN THE CHARACTERIZATION OF LEUKEMIAS.

Blackstock R, Humphrey GB
Dept. Pediatrics, Univ. Oklahoma Health Sciences Center, Oklahoma City, OK, 73190
Methods Cancer Res; 19:3-51 1982

Immunological markers of acute lymphoblastic leukemia (ALL) are reviewed. Methods used to identify receptors or antigens on lymphoid cells and lymphoblasts freshly isolated from human subjecies are emphasized. Rosette studies discussed include E-rosettes, rosettes with mouse erythrocytes, human autologous rosettes, and rosettes with other erythrocytes. Surface and cytoplasmic immunoglobulin, Fc receptors, complement receptors, lymphocyte differentiation antigens, glucocorticoid receptors, peanut agglutinin receptors, and histamine receptors are also discussed. Recent clinical application of immunological markers of ALL only is reviewed with reference to heterogeneity, special variants and relapse ALL, and prognostic significance, although the principles described apply equally well to the use of immunological markers with the myeloid leukemias, the chronic leukemias, and immunodeficiency diseases. Immunological markers required for diagnostic evaluation of ALL are suggested. (421 Refs)

81. BLOCKADE OF THE HUMORAL IMMUNE RESPONSE: IMMUNE COMPLEXES IN CANCER.

Rosen RD, Morgen AC
Dept. Microbiology and Immunology, Baylor Coll. Medicine, Houston, TX, 77221
The Handbook of Cancer Immunology: Volume 9- Humoral Immunity in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 289 pp., 1981.

Patients with early stage cancer who show high levels of soluble immune complexes (ICs) in the serum generally have an unfavorable prognosis. The ICs may contain hidden or blocked antibodies reactive against cultured allogeneic tumor cells. The blocking factors may be anti-idiotype antiglobulins or soluble tumor-associated antigens. However, the nature of the ICs in most patients is unknown. Dogs bearing spontaneous tumors were treated by an immunoadsorption technique, in which the plasma was adsorbed with staphylococcal protein A (SPA). This treatment led to marked tumor necrosis, which was attributed to the unblocking of complement-dependent cytotoxic antitumor antibodies hidden within the circulating ICs. A small group of patients with advanced cancers showed similar good responses to immunoadsorption therapy using SPA. Repeated immunoadsorption therapy might eventually lead to the selection of clones of tumor cells which no longer express surface antigens susceptible to attack by unblocked autologous antibodies. Changes in the expression of surface antigens by the tumor cells could also occur as a consequence of repeated immunoadsorption therapy. This treatment will probably have to be combined with chemotherapy, using agents capable of enhancing the tumor cell injury caused by antibody and complement. These encouraging early results lend support to the experimental data suggesting that host responses to autologous tumors are often blocked by circulating factors having many of the properties of soluble antigens or ICs. (168 Refs)

82. HISTOCOMPATIBILITY AND TUMOR ASSOCIATED ANTIGENS IN SERUM.

Callahan GN, Ferrone S, Allison JP, Reisfeld RA
Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

The fact that major histocompatibility complex (MHC) antigens and tumor-associated antigens (TAA) in human and animal sera can be characterized, suggest that human MHC antigens (HLA systems) are more efficient than cellular antigens in eliciting xenoantibodies to HLA allotypic specificities. These reagents were very valuable in the purification and characterization of HLA antigens of both HLA-A and HLA-B allotypic specificity. If HLA antigens from human sera can be used to sensitize mice to human allotypic specificities, it may be possible to obtain many monoclonal antibodies to allotypic specificities of these antigenic system. Qualitative and/or quantitative changes have been observed in the MHC antigens of both mice and humans in the presence of malignant tumors, suggesting that such sera may be useful in studying the involvement of the MHC in neoplastic transformation. Little information is as yet available on the presence and nature of serum TAAs in cancer patients, primarily because of a lack of specific reagents and sensitive TAA assay systems. However, circulating TAA levels are related to tumor progression in experimental systems, suggesting that monitoring serum TAA levels in cancer patients may be clinically useful. (85 Refs)

83. IMMUNOREGULATION VIA MODIFIED AMINO GROUPS.

Nehlsen-Cannarella SL
Transplantation Immunology Lab., Montefiore Hosp., Medical Center, Albert Einstein Coll. Medicine, Bronx, NY, 10467
The Handbook of Cancer Immunology: Volume 7- Immune Function and Dysfunction in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 372 pp., 1981.

The T-lymphocytes are thought to be the primary mechanism of host defense against tumor growth, although many other cells are involved. Sodium cyanate (NaCNO) blocks antigen recognition by (or the activation of) suppressor T-cells, without apparently affecting the memory cells or the 'homing in' of migrating lymphocytes. NaCNO is specific for the T-cell receptor and does not affect the efferent arc of the immune response. NaCNO is directly toxic to a variety of tumors, selectively inhibiting DNA and protein synthesis. The simultaneous administration of deoxycorticosteroid can cancel the immunosuppressive effects of NaCNO on T-cell helper and cytotoxic killer cells. One major goal of tumor immunotherapy is boosting and steering the aberrant immune response to a pathway leading to the destruction of transformed cells. The success of this treatment depends on the initiation of a tumoricidal immune attack which can kill the tumor before suppressive factors or tumor size can inhibit the immune response. NaCNO may be suitable for such immunotherapeutic protocols. (163 Refs)

84. IMMUNOLOGICAL SURVEILLANCE AND CANCER.

Stutman O
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
The Handbook of Cancer Immunology: Volume 7- Immune Function and Dysfunction in Relation to Cancer. Waters H, ed. New York, Garland STPM Press, 372 pp., 1981.

Analysis of the available evidence on the effects of experimental or clinical immunodeficiency on cancer incidence shows that the orthodox immunosurveillance theory (ie, mediated by a thymus-dependent effector cell system capable of destroying nascent tumors) is wrong. The incidence of most tumors is not increased in thymus-dependent immune deficiencies. Immunosurveillance of a 'nonadaptive' nature may be involved. Macrophages and the non-macrophage natural killer (NK) and natural cytotoxic (NC) cells, which are cytotoxic to tumor cells without specific preimmunization, may be involved in surveillance mechanisms in vivo. These responses may act as putative surveillance devices against non-antigenic tumors, although they are probably not directed against conventional tumor-associated antigens. The fact that most clinical tumors seem to be monoclonal argues against a highly efficient surveillance by either the macrophages or the NK-NC cell system. Procedures interfering with or potentiating macrophage or natural cell-mediated cytotoxicity may provide additional evidence of the efficiency (even the existence) of these in vivo defenses against tumors. Experimental or clinical models of selective deficiencies of macrophage or cell-mediated cytotoxicity may provide additional information. Future research should probably involve experiments designed to determine whether or not immunologic surveillance is mediated by some other mechanism(s). (136 Refs)

85. SUPPRESSOR CELLS OF MAN.

Ellner JJ
Div. Infectious Diseases, Dept. Medicine, Case Western Reserve Univ., Cleveland, OH, 44106
Clin Immunol Rev; 1(1):119-214 1981

Human suppressor cells are discussed with respect to T-cell subsets, functional categorization of suppressor T-cells, suppression by macrophages and prostaglandin-secreting suppressor cells, suppressor cells in infectious diseases, autoimmune disease, immunodeficiency diseases and related conditions, and tumors. Suppressor cells favoring tumor growth and those associated with immunodeficiency (T-cell dysfunction in Hodgkin's diseases and other tumors and B-cell dysfunction in multiple myeloma and other tumors) are reviewed. The role of suppressor cells in immunoregulatory tumors is considered. (304 Refs)

86. NATURAL KILLER (NK) CELLS AND THEIR POSSIBLE ROLES IN RESISTANCE AGAINST DISEASE.

Herberman RB
Lab. Immunodiagnosis, NCI, Bethesda, MD, 20205
Clin Immunol Rev; 1(1):1-65 1981

The characteristics of natural killer (NK) cells and their relation to host resistance to disease are reviewed. Topics discussed include the following: general phenotype of NK cells; expression of markers restricted to NK cells; cell lineage of NK cells; possible relationship of NK cells to T cells, macrophages, or monocytes; interpretation of available evidence regarding lineage of NK cells; possible in vivo roles of NK cells; role of NK cells in resistance against tumor cell lines, primary tumors, microbial infections, and bone marrow transplants; role of NK cells in graft-vs-host disease and in regulation of differentiation of normal hematopoietic or other cells; NK cells as secretory and immunoregulatory cells; clinical correlations of NK cells; and implications of NK cells for immunotherapy. (279 Refs)

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CLINICAL CANCER IMMUNOLOGY AND IMMUNOTHERAPY

SERIES CT06 No. 82/09
SEPTEMBER, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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HE 20. 3173/2:

CLINICAL TRIALS

1. FOLLOW-UP ADJUVANT CHEMOTHERAPY AND CHEMOIMMUNOTHERAPY FOR STAGE II AND III CARCINOMA OF THE BREAST.

Cohen E, Scanlon EF, Caprini JA, Cunningham MP, Oviedo MA, Robinson B, Knox KL
(c/o Scanlon) Dept. Surgery, Evanston Hosp., 2650 Ridge Ave., Evanston, IL, 60201
Cancer; 49(9):1754-1761 1982

Patients with Stage II or III carcinoma of the breast were assigned to one of three adjuvant chemotherapy and chemoimmunotherapy treatment groups following radical or modified radical mastectomy. This study compares the efficacy of single drug treatment (melphalan) versus multiple drug regimens (CFP and CFP + BCG). In the initial phase of the project participants in the melphalan group showed a higher recurrence rate than those in the CFP and CFP + BCG groups. The recurrence rate of the melphalan group was 4.4 times higher than the recurrence rate of the combined polychemotherapy arms. However, after the initial phase, the recurrence rates for the polychemotherapy arms steadily increased and approached the dropping rate of the melphalan group. Currently (247 wk after the beginning of the study and 9 mo after the last patient accrual), 194 patients have been treated (median follow-up time of 101 wk), and no significant differences can be detected between the three treatment arms using any of the following criteria: disease-free interval, proportion of recurrence and recurrence rate. The only factors which are significant with respect to recurrence are the two prognostic factors: tumor size and degree of nodal involvement. The two chemotherapy groups, CFP and CFP + BCG, show no significant difference with respect to recurrence rate along the entire span of the study. (Author abstract) (10 Refs)

2. OBJECTIVE REGRESSIONS OF T- AND B-CELL LYMPHOMAS IN PATIENTS FOLLOWING TREATMENT WITH ANTI-THYMOCYTE GLOBULIN.

Fisher RI, Silver BA, Vanhaelen CP, Jaffe ES, Cossman J
NIH, NCI, Building 10, Room 12N226, 9000 Rockville Pike, Bethesda, MD, 20205
Cancer Res; 42(6):2465-2469 1982

We have conducted a clinical trial utilizing anti-thymocyte globulin (ATG) for the treatment of patients with non-Hodgkin's lymphomas. Six patients were treated; 50% reductions in tumor mass of short duration were observed in one patient with a T-cell lymphoma and two patients with B-cell lymphomas. In vitro assays have been performed in an attempt to study the reactivity and potential mechanisms of antitumor action of the ATG. The ATG bound to essentially all normal blood mononuclear leukocytes as well as tumor cells from patients with T-, B-, or null cell lymphomas demonstrating its lack of specificity. Furthermore, complement-mediated lysis of normal mononuclear leukocytes, normal T- or B-cells, and tumor cells from two unresponsive patients were all comparable; moreover, since this lysis occurred only at concentrations of ATG that are not attainable in vivo, it is unlikely that complement-mediated cytotoxicity accounts for the responses observed. Peripheral blood lymphocyte counts and total erythrocyte rosettes did decrease during ATG treatment. Thus, objective tumor responses in both B- and T-cell non-Hodgkin's lymphomas can be achieved with a very nonspecific antiserum although significant toxicity resulted. Whether the magnitude or duration of response can be increased with monoclonal antibodies remains to be determined. Future success with serotherapy might require use of either a battery of different monoclonal antibodies or a single monoclonal antibody that can deliver radioisotopes, chemotherapy, or toxins to the tumor cells. (Author abstract) (13 Refs)

3. ADJUVANT CHEMOIMMUNOTHERAPY STAGE I/II MALIGNANT MELANOMA.

Knost JA, Reynolds V, Greco FA, Oldham RK
NCI-Fredrick Cancer Res. Center, Fredrick, MD, 21701
J Surg Oncol; 19(3):165-170 1982

Sixty patients with Stage I or Stage II malignant melanoma were treated with wide local excision of the primary and dissection of the regional lymph nodes prior to being randomized to chemoimmunotherapy with dacarbazine plus intradermal BCG vs semustine plus intradermal BCG. For the 32 Stage I patients, there were no differences in survival between the two treatment groups. Survival was similar to a concomitant control group of 45 Stage I patients. For Stage II melanoma both chemoimmunotherapy groups had a significantly better survival than the 11 patients in the untreated control group. These results do not indicate that this form of chemoimmunotherapy is valuable in Stage I malignant melanoma but further trials are needed for patients with Stage II disease. (Author abstract) (49 Refs)

4. CLINICAL EFFECT OF CONCOMITANT USE OF NON-SPECIFIC IMMUNOPOTENTIATION ON 172 CASES OF PRIMARY LUNG CANCER (STAGE III, IV) TREATED WITH RADIATION COMBINED WITH CHEMOTHERAPY.

Hiyoshi Y, Ogawa Y, Imajo Y
Dept. Radiology, Kobe Univ. Sch. Medicine, Kobe, Japan
Nippon Gan Chiryo Gakkai Shi; 16(7):1384-1896 1981

Clinical effects of concomitant administration of the immunopotentiating agents picibanils (OK-432) and polysaccharide-Kureha (PSK) were studied in 91 Stage III and 81 Stage IV primary lung cancer patients treated with radiation and chemotherapy. The clinical effects observed in the patients administered the combination OK-432 + PSK were compared with those observed in the patients who were administered the OK-432 or the PSK alone and with those who were not administered either. Fifty-percent survival periods of the 12 Stage III patients given OK-432 + PSK, the 27 given OK-432 alone, the 24 given PSK alone, and the 28 not given either were 14.4, 12.2, 9.0, and 7.5 mo, respectively. One-yr survival rates of the Stage III patients given OK-432 or OK-432 + PSK were significantly higher than those for the patients given neither agent. The 50% survival periods of the 8 Stage IV patients given OK-432 + PSK, the 24 given OK-432 alone, the 13 given PSK alone, and the 36 not given either were 5.0, 7.0, 7.6, and 3.3 mo, respectively. No significant differences in 1-yr survival rates were observed between any of the groups of Stage IV patients. The 50% survival periods were increased in the 74 squamous cell carcinoma patients treated with OK-432 or OK-432 + PSK and in the 41 adenocarcinoma patients treated with any of the immunotherapies. Long-term administration of OK-432 + PSK was recommended for patients with Stage III primary lung cancer treated with radiation and chemotherapy. (45 Refs) (In JPN)

5. CHEMOIMMUNOTHERAPY IN CARCINOMA OF THE LUNG.

Carabasi RA, Rosato FE, El-Mahdi A, Langley J
Dept. Surgery, Jefferson Medical Coll., Thomas Jefferson Univ., Philadelphia, PA

Curr Surg; 39(2):85-88 1982

A prospective, non-randomized, nonstratified study of the effects of BCG and cyclophosphamide (CP) in 52 patients (35 men, 17 women, 40-78 yr old) with non-oat cell carcinoma of the lung is reported. Twenty-two patients had Stage I and II disease, and 30 had Stage III disease. The cell types were evenly distributed between adenocarcinoma and squamous carcinoma in all groups. Sixteen patients had inoperable tumors; the remaining 36 underwent thoracotomy. All patients with Stage III disease received full-course x-ray therapy (4,500 rad in 20 fractions) before starting chemoimmunotherapy. One mo after surgical resection and/or radiotherapy, patients began receiving CP (50 mg/day, po), and BCG injections given 2x/mo. This regimen was continued for 1 yr. Nineteen of 22 clinical Stage I-II patients were currently alive without evidence of active disease. Ten of 19 completed 1 yr of chemoimmunotherapy and were not currently in the protocol, while the remaining 9 were treated from 2-10 mo. Three patients died of recurrent disease. Twelve of 27 Stage III patients were currently alive and well, and 5 had completed 1 yr of therapy. Five of 15 patients who died completed 1 yr of therapy; the other 10 had rapidly advancing disease and died of their illness after 3-10 mo of treatment. T-cell levels correlated with the extent of disease and the response to treatment. Skin tests were of no help in assessing prognosis. A statistically significant increase in 1-yr-survival rate was observed in patients with Stage I and Stage II disease. Results indicate that chemoimmunotherapy may favorably influence the course of Stage I and Stage II non-oat cell carcinoma of the lung when compared with surgical treatment alone. (5 Refs)

6. FIVE-YEAR RESULTS OF A CONTROLLED STUDY OF BCG IMMUNOTHERAPY AFTER SURGICAL RESECTION IN BRONCHOGENIC CARCINOMA.

Millar JW, Roscoe P, Pearce SJ, Ludgate S, Horne NW
Chest Unit, City Hosp., Greenbank Drive, Edinburgh EH10 5SB, Scotland

Thorax; 37(1):57-60 1982

Ninety-two patients with histologically confirmed bronchogenic carcinoma treated by surgical resection of the tumor were subsequently given immunotherapy with BCG (Glaxo). The patients were randomly allocated into three groups. Twenty-nine patients received multipuncture BCG (50 to 250 x 10(6) viable units), and 26 patients intradermal BCG (0.4 to 0.9 x 10(6) viable units), treatment being given at 1, 2, 5, 9, 13, 26, and 52 wk after operation. Thirty-seven control patients did not receive any BCG immunotherapy; 2 patients in the control group were lost to follow-up. The overall 5-yr survival in all groups was 37%. Favorable prognostic features were squamous carcinoma (45% 5-yr survival), the absence of involved mediastinal nodes at operation (46%), and lobectomy (45%), but even the presence of involved mediastinal nodes was associated with a 19% 5-yr survival. There were no statistically significant differences between the survival of the control group and either group treated by immunotherapy considered individually or in combination. The influence of the presence of positive mediastinal lymph nodes and the extent of surgical resection on survival was not affected by immunotherapy. No serious side-effects of immunotherapy were encountered. (Author abstract) (20 Refs)

7. PHASE-1 CLINICAL TRIAL OF MONOCLONAL ANTIBODY IN TREATMENT OF GASTROINTESTINAL TUMOURS.

Sears HF, Atkinson B, Mattis J, Ernst C, Herlyn D, Steplewski Z, Hayry P, Koprowski H
(c/o Koprowski), Wistar Inst., 36th St. at Spruce, Philadelphia, PA, 19104

Lancet; 1(8275):762-765 1982

A Phase-I clinical trial of a murine monoclonal antibody that specifically suppresses growth of human gastrointestinal tumors in athymic mice was conducted in four patients, who were given 15-200 mg purified antibody. The monoclonal antibody persisted in the circulation for more than a week when more than 15 mg was given. Antibodies against mouse immunoglobulin developed in three of the four patients. In one patient who received autologous mononuclear cells that had been mixed with monoclonal antibody by way of a hepatic-artery catheter, hepatic metastases became smaller and their echogenic characteristics changed, and there was heavier monocyte infiltration in the histological appearance of a resected metastasis. (Author abstract) (15 Refs)

8. GASTRECTOMY COMBINED WITH SPLENECTOMY AND IMMUNOTHERAPY FOR ADVANCED GASTRIC CANCER PATIENTS.

Miwa H, Kojima K, Tsurumi T, Orita K
First Dept. Surgery, Okayama Univ. Sch. Medicine, Okayama, Japan

Nippon Gan Chiryo Gakkai Shi; 16(7):1365-1370 1981

Postoperative cellular immunity and prognosis of 60 advanced gastric cancer patients (Group A) who were treated with gastrectomy combined with splenectomy were compared with those of 81 such patients (Group B) who were treated with gastrectomy alone. According to stage, 43 Group A and 74 Group B patients had Stage III cancer, and 17 Group A and 7 Group B patients had Stage IV. The splenectomies were performed because of the presence of metastatic lymph nodes and serosal invasion that was discovered during the surgery. Immunotherapy using levamisole (LMS; 150 mg/day, 3 days, po) was given to 18/60 patients who underwent splenectomy. Cellular immunity was investigated using blastogenic response of peripheral blood to phytohemagglutinin (PHA), peripheral lymphocyte counts, and skin responses to purified protein derivative or PHA. Lymph node metastases, particularly of the Number 10 lymph nodes, were more frequent in the Group A patients than in the Group B. Cellular immunity after surgery, compared to that before, decreased in the Group A patients who were not administered the LMS, but increased in the Group A patients who were administered the LMS. Three-yr actuarial survival rate of the Group A patients was 15% less than that of the Group B patients, but the Group A patients had more advanced gastric cancers than the Group B patients. Group A patients who were also administered immunotherapy had survival rates approaching those of the Group B patients. Splenectomy, combined with immunotherapy using LMS or some other drug, should be performed in patients with advanced gastric cancer if lymph node (Number 10 or 11) metastasis or serosal invasion is observed. (17 Refs) (In JPN)

9. TOLERANCE TEST WITH HUMAN LYMPHOCYTOBLAST INTERFERON. CONTROLLED STUDY IN 3-YEAR SURVIVAL OF PATIENTS WITH OSTEOSARCOMA.

Kotz R, Plattner E, Ramach W, Flener R, Bodo G
Orthopadische Universitatsklinik, Garnisongasse 13, A-1090 Wien, Austria
Arzneim Forsch; 32(4):446-448 1982

In eight patients with osteosarcoma we conducted a controlled tolerance study with human lymphoblast interferon. Interferon was applied for 12 mo and the control period after stopping interferon has lasted 12-42 mo up to now. Four out of eight patients who received interferon did not show any adverse reaction concerning clinical and laboratory tests during the course of a 1-yr application and during the follow-up period, respectively. Only reversible thrombopenias and an increase in the alpha2-globulins fraction were observed in the interferon and in the control group, respectively. All of the eight patients have up to now survived tumor-free. (Author abstract) (10 Refs) (In GER)

10. PHASE I TRIALS OF MURINE MONOCLONAL ANTIBODIES TO TUMOR ASSOCIATED ANTIGENS: PRELIMINARY OBSERVATIONS.

Dillman RO, Sobol RE, Royston I
Dept. Medicine, Univ. California, San Diego, CA, 92161
Protides Biol Fluid Proc Colloq; 29:915-920 1982

Murine monoclonal antibodies (MoAbs) to tumor-associated antigens were infused into two patients with chronic lymphocytic leukemia (CLL) and two melanoma patients with advanced malignancies refractive to standard therapy. Prior to treatment, MoAb reactivity was confirmed in vitro with the patients' CLL cells or melanoma tissue. T101, an IgG2A produced by immunizations with T cell leukemia line 8402, was given to one CLL patient at doses of 1 and 3 mg on successive days then 12 mg 2 wk later, and a single 10 mg dose was given to the other CLL patient. Both melanoma patients were given single 10 mg infusions of M225, an IgGa2 produced by immunization with the M21 melanoma cell line. In circulating CLL cells, after infusion of T101, there was an immediate, marked decrease in lymphocyte number that reached a max in 2 hr, then rapidly increased. Serum MoAb had disappeared from circulation by 4 hr. Since T65 antigen persisted throughout the test period, no significant antigen modulation associated with leukemia cell recovery occurred. In melanoma patients, while no in vivo binding to tumor was demonstrated, M225 levels were still detectable 24 hr after infusion. Significant systemic reactions occurred with 10 and 12 mg infusions of T101; all resolved after administration of fluids and epinephrine. (17 Refs)

SYNTHETIC IMMUNOTHERAPEUTIC AGENTS

11. CP-46,665-1: A NOVEL LIPOIDAL AMINE WITH ANTIMETASTATIC AND IMMUNOMODULATORY PROPERTIES.

Wolff JS, Hemsworth GR, Kraska AR, Hoffman WW, Figdor SK, Fisher DO, Jakowski RM, Niblack JF, Jensen KE
(c/o Jensen) Pfizer Central Res., Groton, CT, 06340
Cancer Immunol Immunother; 12(2):97-103 1982

Antimetastatic and immune effects and toxicity of [4-aminomethyl-1(2, 3-(di-n-decyloxy)-n-propyl)-4-phenylpiperidine dihydrochloride] (CP-46,665-1) were examined. Single iv injection of 0.6-10.0 mg CP-46,665-1/kg 1 day after amputation of B-16 melanoma-bearing legs of B6D2F1 mice decreased the number of metastatic lung lesions, with no lesions evident in 31-44% of mice as compared with 0-13% of untreated controls. The optimal single dose range was 0.6-2.5 mg/kg. Repeated administrations enhanced antimetastatic effect. Preoperative CP-46,665-1 administration had less antimetastatic effect. Concomitant postoperative administration of cyclophosphamide and CP-46,665-1 showed no change in antimetastatic effect. Seventy percent of rats survived 100 days following implantation 13762 mammary adenocarcinoma after administration of 0.6 mg CP-46,665-1, as compared with 10% of untreated controls. Of the survivors, 100% of untreated and 0 of treated rats showed visceral metastases. CP-46,665-1 was devoid of interferon-inducing activity. Pretreatment of mice with x-irradiated L-1210 leukemia cells was immunogenic; addition of CP-46,665-1 to the vehicle further increased the mean survival times of recipient mice. CP-46,665-1 accumulated primarily in the liver, spleen, lung, bone marrow, and lymph nodes. When CP-46,665-1 (1, 5, and 25 mg/kg iv, once every 4 days for 3 mo) in Intralipid was administered to rats and dogs, good toleration was observed at the 1 and 5 mg/kg doses. At the 25 mg/kg dose, animals exhibited side effects including mild progressive anemia, increased RBC fragility, and hematuria. The results indicated that CP-46,665-1 has potent antimetastatic and reticuloendothelial system-stimulatory effects and is well-tolerated in animals. (10 Refs)

INTERFERON

12. INTERFERON EFFECT ON CYTOTOXICITY OF PERIPHERAL BLOOD AND TUMOR-ASSOCIATED LYMPHOCYTES AGAINST HUMAN OVARIAN CARCINOMA CELLS.

Allavena P, Introna M, Sessa C, Mangioni C, Mantovani A
(c/o Mantovani), Istituto di Ricerche Farmacologiche 'Mario ONegri', via Eritrea 62, 20157 Milan, Italy
JNCI; 68(4):555-562 1982

A study was done to investigate the tumoricidal activity of peripheral blood lymphocytes (PBL) and tumor-associated lymphoid cells (TAL) against freshly isolated tumor cells in human ovarian carcinoma. TAL and carcinoma cells were purified by density and velocity sedimentation on discontinuous Ficoll-Hypaque gradients and fetal bovine serum. Purified carcinoma cells from 23 ascitic and 3 solid tumors were used as targets in a 4-or a 20-hr 51Cr release assay. K562 cells were used to measure natural killer (NK) activity. Freshly purified ovarian carcinoma cells were relatively resistant to lysis by normal unstimulated PBL. Cytolytic activity of ovarian cancer PBL and TAL did not exceed that of control PBL; only one PBL preparation had high levels of cytotoxicity (36.2 and 42.9% specific lysis after 4 and 20 hr at an effector-to-target cell ratio of 50:1) against autologous cancer cells but not against allogeneic targets (less than 5% specific lysis). TAL and, to a lesser extent, ovarian cancer PBL showed impaired NK activity against K562 compared to the activity seen in controls. In vitro exposure to partially purified human fibroblast interferon (IFN: 1,000 U/ml for 1-18 hr) augmented NK activity against K562 of PBL and TAL. When ovarian carcinoma cells were used as targets, IFN enhanced the cytotoxicity of normal PBL in a 4-and 20-hr assay; stimulation by IFN was less frequently observed with ovarian cancer PBL and

TAL in a 4-hr assay, but after 20 hr effector cells from tumor-bearing subjects showed IFN-boosted cytotoxicity against carcinoma cells similar to the degree of cytotoxicity seen in controls. IFN enhanced the cytotoxicity of PBL and TAL against both autologous and allogeneic carcinoma cells. Thus PBL and TAL are rarely cytotoxic against 51Cr-labeled fresh autologous carcinoma cells, but in vitro exposure to IFN induced low levels of killing of ovarian tumor cells. (Author abstract) (18 Refs)

13. ALPHA INTERFERON AND ACYCLOVIR TREATMENT OF HERPES SIMPLEX VIRUS IN LYMPHOID CELL CULTURES.

Hammer SM, Kaplan JC, Lowe BR, Hirsch MS
Infectious Disease Unit, Dept. Medicine, Massachusetts General Hosp., Boston, MA, 02114
Antimicrob Agents Chemother; 21(4):634-640 1982

The T-lymphoblastoid cell line CEM, persistently infected with herpes simplex virus type 1, has been used to examine the antiviral efficacy of human alpha interferon and acyclovir, both alone and in combination. Acyclovir and interferon each produced dose-dependent decreases in virus titer at concentration ranges of 1 to 100 uM (approx 0.225 to 22.5 ug/ml) and 10 to 10,000 U/ml, respectively. Mean reductions in titer of 1.9 and 4.2 log10 PFU/ml were observed with 100 uM acyclovir and 10,000 U of interferon per ml, respectively, on day 10 of treatment. The combination of 100 uM acyclovir and 10,000 U of interferon per ml produced the most rapid fall in virus titer of all regimens examined and elimination of infectious virus by day 7. Prolonged treatment (greater than 10 days) with acyclovir or alpha interferon was accompanied by a gradual return of virus titer to control levels despite the continuous presence of drug. Virus preparations isolated from such cultures were tested for antiviral agent sensitivity by a plaque reduction method. Acyclovir-exposed isolates were found to be acyclovir resistant, with 50% inhibitory doses of greater than 200 uM, and to be thymidine kinase deficient. Alpha interferon-exposed isolates were not interferon resistant. These results suggest that, in persistently herpes simplex virus-infected CEM cells: (i) combination treatment with 100 uM acyclovir and 10,000 U of alpha interferon per ml is more effective in reducing virus titer than either agent alone; (ii) prolonged exposure to drug may result in development of resistance by either the virus strain or the host cell system; and (iii) development of acyclovir resistance by herpes simplex virus in lymphoid cells is mediated by thymidine kinase. (Author abstract) (37 Refs)

14. GENETIC ANALYSIS OF THE ROLE OF CAMP IN MEDIATING EFFECTS OF INTERFERON.

Schneck J, Rager-Zisman B, Rosen OM, Bloom BR
Dept. Microbiology and Immunology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Proc Natl Acad Sci USA; 79(6,part1):1879-1883 1982

The effects of interferon (IFN) on Fc receptor-mediated phagocytosis, intracellular cAMP levels, antiviral activity, and growth inhibition were analyzed in a cloned macrophage-like cell line, J774.2, and variants derived from it. Purified IFN increased Fc receptor-mediated phagocytosis in J774.2 cells, and in cAMP-responsive nonphagocytic variants but was without effect in cAMP-unresponsive nonphagocytic variants, in adenylate cyclase-deficient variants, and in cAMP-dependent protein kinase-deficient variants. Under conditions in which IFN augmented phagocytosis, it increased intracellular levels of cAMP. Parental cells were highly sensitive to IFN-mediated growth inhibition. In contrast, cAMP-dependent protein kinase-deficient variants were only 1/100th as sensitive to growth inhibition by IFN. All cell lines tested, both responsive and unresponsive to cAMP, were equally protected by IFN against infection with vesicular stomatitis virus, demonstrating that the antiviral state was independent of cAMP. These results indicate that, in transformed macrophages, stimulation of phagocytosis and inhibition of growth by IFN are mediated through intracellular cAMP, whereas the antiviral state induced by IFN is independent of cAMP. (Author abstract) (31 Refs)

15. REGULATION OF 2-5 A SYNTHETASE ACTIVITY AND ANTIVIRAL STATE IN INTERFERON TREATED CHICK CELLS.

Lab M, Thag M, Soteriadou K, Koehren F, Justesen J
Faculte' de Medicine, Laboratoire de Virologie et Groupe de Recherches de INSERM U74, rue Koeberle, 6700 Strasbourg, France
Biochem Biophys Res Commun; 105(2):412-418 1982

The activity of 2'-5'oligoadenylate synthetase (2-5 A synthetase) and the antiviral state (AVS) of chick embryo fibroblasts following interferon (IFN) treatment were investigated. 2-5 A synthetase increased during IFN treatment and rose to a maximun level in 5-6 hr, remaining at this level as long as IFN was present in the culture medium. The AVS, measured by the inhibition of Sindbis virus yield, exhibited similar kinetics. Following removal of IFN, both the 2-5 A synthetase activity and the AVS were maintained for 9-10 hr, after which the activity decayed. If cycloheximide was added to the culture immediately following removal of IFN, this decay was not observed; both activities remained at the 5-6 hr peak level. This effect suggests that the decrease of 2-5 A synthetase is controlled by an unstable regulatory protein. To test if this regulation is due to either degradation of 2-5 A synthetase or reversible activation, the cells were treated for 6 hr with IFN, the IFN removed for the next 24 hr, and cycloheximide then added at 30 hr. For both the 2-5 A synthetase and AVS, removal of IFN again lead to a decay; however, inhibition of protein synthesis by cycloheximide at 30 hr produced an increase in both activities to the same level as when IFN was removed at 6 hr. This further suggests that an unstable protein reversibly inactivates the enzyme activity. In the same experiments, removal of cycloheximide after 18 hr produced a 'superinduction', an increase in the 2-5 A synthetase activity and AVS. This may be explained by the accumulation of mRNA for 2-5 A synthetase during the period of cycloheximide treatment, this mRNA being transiently inactivated by factors which require protein synthesis. (17 Refs)

16. CHROMOSOMAL LOCATION OF A HUMAN ALPHA INTERFERON GENE FAMILY.

Slate DL, D'Eustachio P, Pravtcheva D, Cunningham AC, Nagata S, Weissmann C, Ruddle FH
Cancer Metastasis Research Group, Pfizer Central Research, Groton, CT, 06340
J Exp Med; 155(4):1019-1024 1982

A series of human/rodent somatic cell hybrids were scored for the presence of DNA sequences hybridizing to an alpha-1 interferon DNA probe. Hybrids were generated by fusing Chinese hamster E36 cells with human BD melanoma cells, temperature-sensitive Chinese hamster ovary cells and human WBC, mouse A9 cells with GM17 human fibroblasts, or mouse A9 cells with GM589 human fibroblasts. Hybrids were karyotyped and tested for the presence of human marker isozymes. In human/Chinese hamster hybrid cells, sequences hybridizing to the human alpha1 interferon probe were clearly observed in cellular DNA when chromosome 9 was retained. In hybrids lacking chromosome 9, no human-specific bands were observed. Segregation of chromosome 9 below a frequency of 20-30% resulted in a failure to detect alpha1 interferon related sequences. With appropriate cell hybrids, it should be possible to map rodent alpha interferon-related DNA sequences. (25 Refs)

17. INDUCTION OF INTERFERON-GAMMA IN MOUSE SPLEEN CELLS BY OK-432, A PREPARATION OF STREPTOCOCCUS PYOGENES.

Saito M, Ebina T, Koi M, Yamaguchi T, Kawade Y, Ishida N
Dept. Bacteriology, Tohoku Univ. Sch. Medicine, 2-1 Seiryo-machi, Sendai 980, Japan
Cell Immunol; 68(1):187-192 1982

A bacterial antitumor and immunopotentiating agent, OK-432, induced interferon in the spleen cell cultures but not in the thymus cell cultures of various inbred strains of mice. When 1 x 10(7) spleen cells were cultured in the presence of 5 ug/ml of OK-432, interferon activity was detected as early as 4 hr later and reached a maximum level of about 160 to 500 units/ml 24 hr later. OK-432-induced interferon was mainly an IFN-gamma of mol wt approximately 40,000, but also contained interferon-alpha and interferon-beta. (Author abstract) (22 Refs)

MICROBIAL FRACTIONS AND EXTRACTS

18. PREPARATION AND ANTITUMOR ACTIVITY OF NONTOXIC LIPID A.

Ribi E, Amano K, Cantrell J, Schwartzman S, Parker R, Takayama K
Ribi Immuno Chem Res., Inc., P.O. Box 1409, Hamilton, MT, 59840
Cancer Immunol Immunother; 12(2):91-96 1982

The isolation of endotoxin B5 from the endotoxic extract ReGl-PCP from Salmonella typhimurium strain G30/C21, a heptose-less mutant, and the effects of B5 on line-10 hepatocellular carcinomas in guinea pigs was examined. B5 combined with trehalose dimycolate (P3) produced line-10 tumor regression in only 1/26 guinea pigs unless an essentially nontoxic peptide-containing side-fraction (ACP) recovered during isolation of B5 was added. Addition of ACP produced a cure rate of 81% (54/67 guinea pigs). Two cycles of treatment of B5 with 20 mM sodium acetate at 100 C for 30 min caused the removal of 99% of the 2-keto-3-deoxyoctonate (KDO) content without loss of toxicity or tumor-regressive potency indicating. More drastic treatment of B5 led to a product, B5-HCl, which was also depleted of KDO but was essentially nontoxic and not pyrogenic. B5-HCl produced cures in 27/32 tumor-bearing guinea pigs. Results of chemical analyses showed that glucosamine and total fatty acid content of the toxic B5-pH 4.5 and the nontoxic B5-HCl were essentially the same, but the nontoxic B5-HCl was significantly lower in phosphorus content. Thin layer chromatography revealed that B5-HCl contained components of lower polarity. The results suggested that loss of toxicity was due to removal of the acid-labile phosphate group. Inoculation of combined B5 and N-acetyl-muramyl-L-seryl-D-isoglutamine (MDP) killed 3/5 guinea pigs, while combination of B5-HCl and MDP caused neither lethargy nor death. It was suggested that B5-HCl is a potential candidate for immunotherapy of human cancer. (23 Refs)

19. STUDIES OF THE PROPERTIES OF A STREPTOCOCCAL PREPARATION OK-432 (NSC-B116209) AS AN IMMUNOPOTENTIATOR. II. MECHANISM OF MACROPHAGE ACTIVATION BY OK-432.

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Cancer Immunol Immunother; 12(2):141-146 1982

The ability of the streptococcal preparation OK-432 to induce the cytotoxic activity of plastic-adherent mouse peritoneal exudate cells (PEC) through activation of the third component (C3) of complement was examined. C3 binding to OK-432 increased linearly with increasing OK-432 concentrations. When EDTA was used to prevent C3 activation, little binding was observed. Radiolabelling and immunofluorescence studies indicated that C3-OK-432 complexes bind to PEC through the C3 receptors. PEC pretreated with C3-OK-432 markedly reduced the uptake of 3H-thymidine by MM2 mouse mammary tumor cells in the presence of resident PEC. PEC pretreated with OK-432 did not cause such a marked reduction of the uptake suggesting that C3-OK-432 complexes trigger cytostatic activity of resident PEC through binding of complexes to the C3 receptor sites of the PEC. PEC from mice pretreated with OK-432 showed cytostatic activity and MM2 tumor growth inhibition. The mechanism of PEC (presumably macrophages) activation by OK-432 is discussed. (23 Refs)

CYTOKINE THERAPY

20. AUGMENTATION OF THE ANTI-TUMOR THERAPEUTIC EFFICACY OF LONG-TERM CULTURED T LYMPHOCYTES BY IN VIVO ADMINISTRATION OF PURIFIED INTERLEUKIN 2.

Cheever MA, Greenberg PD, Fefer A, Gillis S
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J Exp Med; 155(4):968-980 1982

C57BL/6 mice bearing disseminated FBL-3 (a transplanted ascitic Friend's virus-induced leukemia) were treated with cyclophosphamide (CY: 180 mg/kg) and long-term cultured T lymphocytes (CTL) plus purified interleukin 2 (IL-2: 80 units/day). The long-term cultured T lymphocytes were highly cytotoxic to FBL-3, but not to an antigenically distinct C57BL tumor, EL-4(G-). CTL continued to proliferate in vitro and expand in number when repeatedly exposed to IL-2 in vitro; however, when cultured without IL-2, less than 10% remained viable at 72 hr. Gamma-irradiation reduced the number of viable cells to less than 5% at 72 hr, even in the presence of IL-2. When IL-2 was administered in vivo to mice with FBL-3 tumors, no detectable antitumor effect was observed, even with CY. Therapy on day 5 after tumor inoculation with CY plus CTL (5 x 10(6)) prolonged survival of mice but produced no cures. Treatment with CY plus CTL plus IL-2 on days 5-9 cured 11/16 mice. Thus, as an adjunct to CY, CTL were effective in tumor therapy, and their efficacy was significantly augmented by inoculation of exogenous IL-2. The in vivo efficacy of exogenous IL-2 in adoptive chemoimmunotherapy required that the effector cell be capable of proliferating in the host. While noncultured immune cells were effective in antitumor therapy, their efficacy was not augmented by exogenous IL-2. It is suggested that IL-2 promotes in vivo growth and/or survival of adoptively transferred cells. (41 Refs)

21. INTERLEUKIN 1 AND T CELL ACTIVATION.

Mizel SB
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Immunol Rev; 63:51-72 1982

The characterization and role of interleukin 1 (IL 1) in T cell activation is reviewed. IL 1 appears to be the macrophage-derived mediator needed to initiate and amplify all T cell-dependent immune responses and to induce inflammatory mediators. IL 1 also induces the synthesis and secretion of interleukin 2, which is an essential element for T cell activation involving converting a primary maturational signal from macrophages into a secondary proliferative signal from T cells. (62 Refs)

22. INTERLEUKIN 1, A POTENTIAL REGULATOR OF FIBROBLAST PROLIFERATION.

Schmidt JA, Mizel SB, Cohen D, Green I
Lab. Immunology, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
J Immunol; 128(5):2177-2182 1982

Secondary mixed lymphocyte reaction (MLR) supernatants contain factors that stimulate fibroblast proliferation in vitro. Biochemical analysis of secondary MLR supernatants using gel filtration chromatography and isoelectrofocusing (IEF) demonstrated that the fibroblast proliferation factors have apparent mol wt of 75,000 and 13,000 and isoelectric points (pI) of 6.8 to 7.2, 5.8 to 6.2, and 5.2 to 5.4, values similar to those previously reported for human interleukin 1 (IL 1). To further explore the relationship between the MLR-derived fibroblast proliferation factors and IL 1, the following experiments were performed. First, the fractions obtained from gel filtration and IEF were assayed for both thymocyte proliferation activity, a measure of IL 1 activity, and fibroblast proliferation activity, and superimposable activity profiles were obtained. Second, to confirm that the observed thymocyte proliferation activity was in fact due to IL 1 and not interleukin 2 (IL 2) or novel factors, the IEF fractions contained peak thymocyte and fibroblast proliferation activity (ie, fractions having pI of 6.8, 6.0, and 5.3, respectively) were demonstrated to stimulate IL 2 production by a murine T lymphoma line, a specific measure of IL 1 activity. Third, IL 1 and the fibroblast proliferation factors were co-purified through a three-step, 200-plus-fold purification protocol consisting of ammonium sulfate precipitation, gel filtration chromatography, and IEF. Fourth partially purified human IL 1 made in another laboratory and highly purified murine IL 1, but not human and murine IL 2, stimulated fibroblast proliferation. These results demonstrate that the fibroblast proliferation factors found in secondary MLR supernatants have several functional and biochemical properties in common with human IL 1. These findings raise the possibility that IL 1 may regulate fibroblast proliferation and that the local production of IL 1 by infiltrating mononuclear cells may contribute to the fibrosis observed in chronic inflammatory disease states. (Author abstract) (55 Refs)

23. MECHANISM OF T CELL ACTIVATION: ROLE AND FUNCTIONAL RELATIONSHIP OF HLA-DR ANTIGENS AND INTERLEUKINS.

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Immunol Rev; 63:73-110 1982

The mechanism by which non-activated T-lymphocytes become sensitive to interleukin 2 (IL2) is reviewed. T cells appear to be sensitized to IL 2 during activation by HLA-DR antigens by the induction of IL-2 receptors, which occurs when foreign antigen from antigen-presenting cells plus HLA-DR molecules interact with the corresponding T cell receptors. Studies on the control of IL-2 synthesis are reviewed in various systems. (83 Refs)

24. EFFECT OF ADRENORECEPTOR BLOCKADE ON HEMORRHAGIC NECROSIS OF METH A SARCOMATA INDUCED BY ENDOTOXIN OR TUMOR NECROSIS SERUM.

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Immunopharmacology; 4(2):163-171 1982

The effects of alpha- and beta-adrenoreceptor blockade on the induction of hemorrhagic necrosis in Meth A sarcoma by endotoxin (ET) and tumor necrosis serum (TNS) are reported. TNS and normal mouse serum (NMS) were prepared in approx 14 wk old female Swiss random bred mice (wt approx 30 g). Tumor experiments were performed with approx 12 wk old female BALB/c mice (wt approx 20 g). Mice with 9-day-old Meth A sarcomata received an ip injection with graded doses of phentolamine, propanolol, or saline followed by 25 ug ET. ET alone induced a significant reduction of the mean tumor size compared to the saline-treated controls. Two out of 5 mice had complete regression of their tumors. Neither dose of phentolamine, when given prior to ET, altered the mean tumor growth significantly. Propanolol did not substantially change the effects of ET on tumor growth, but the highest dose, 50 mg/kg potentiated the effect of ET. The effects of phenoxybenzamine (PBA) are presented. PBA given prior to ET reduced the antitumor effect of ET considerably. At day 14 the mean tumor size of animals treated with PBA and ET was in the range of the saline-treated controls, without any apparent relation to dose effect. PBA tends to induce a dose-dependent decrease of the extent of necrosis. Following an injection of saline or adrenoreceptor antagonist, tumor-bearing mice were injected iv with 0.2 or 0.5 ml TNS or NMS. A small quantity of TNS induced hemorrhagic necrosis in 3 out of 5 animals. pretreatment with phentolamine or PBA completely prevented the induction of hemorrhagic necrosis by 0.2 ml TNS. No tumor regression was induced by TNS in the experiments. (16 Refs)

25. T CELL REPLACING FACTORS IN THE B CELL RESPONSE TO ANTIGEN.

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Dept. Biology, Univ. California, San Diego, La Jolla, CA, 92093

Immunol Rev; 63:111-128 1982

Experiments on the isolation and characterization of T cell replacing factor (TRF) from a long-term alloreactive T cell line, C.C3.11.75, are described. The activity found in this line was studied in an 'IL2 synergy' assay and given the provisional name (DL)TRF. B cells from certain lines did not respond to this TRF, which was not interleukin 1 or 2. This TRF can increase the frequency of induced B cell proliferation, act on a single B cell, and is necessary for immunoglobulin secretion in one model. (34 Refs)

26. MURINE EPIDERMAL CELL-DERIVED THYMOCYTE-ACTIVATING FACTOR RESEMBLES MURINE INTERLEUKIN 1.

Luger TA, Stadler BM, Luger BM, Mathieson BJ, Mage M, Schmidt JA, Oppenheim JJ
Natl. Inst. Dental Res., NIH, Room 324, Building 30, Bethesda, MD, 20205
J Immunol; 128(5):2147-2152 1982

We have previously described an epidermal cell-derived thymocyte-activating factor (ETAF), which is produced by the murine PAM 212 keratinocyte cell line. ETAF appeared to be similar to macrophage-derived interleukin 1 (IL 1) in its biologic activities and biochemical characteristics. Both IL 1 and ETAF augment thymocyte proliferation, enhance lymphocyte production of interleukin 2 (IL 2), and are 15,000 mol wt polypeptides that are stable at pH 4 to 11 and from-70 C to 60 C. In this study we describe a quantitative microassay to obtain standardized assessment of ETAF activity, which enabled us to further define the characteristics of ETAF and its relationship to IL 1. Just as stimulated macrophages produce more IL 1 activity, Pam 212 keratinocyte production of ETAF activity was increased by stimulation with lipopolysaccharide (LPS) or silica. Increased levels were also obtained by mechanical disruption of confluent monolayers of keratinocytes and by blocking proliferation of the Pam 212 cells with hydroxyurea at the G1/S interphase. These observations in conjunction with a concomitant decrease in keratinocyte viability suggest that 'injurious' stimuli that prolong the G1 phase of the cell cycle favor ETAF production. ETAF, like murine IL 1, has an isoelectric point of 5.2. The same subpopulations of PNA- thymocytes that respond to PHA and IL 1 are responsible for the enhanced proliferative response to ETAF. Furthermore, as in the case of IL 1, PNA- Lyt-2-thymocytes were most responsive to ETAF, but not PNA+ Lyt-2+ thymocytes. Finally, ETAF activity, like IL 1, appears to be a mitogenic signal for fibroblasts. Although produced by different cell types, these observations continue to support the view that ETAF may be identical or closely related to IL 1. (Author abstract) (33 Refs)

THYMIC HORMONES AND OTHER IMMUNORESTORATIVE AGENTS

27. IDENTIFICATION OF HUMAN THYMIC EPITHELIAL CELLS WITH ANTIBODIES TO THYMOSIN ALPHA IN MYASTHENIA GRAVIS.

Dalakas MC, Engel WK, McClure JE, Goldstein AL, Askanas V
NIH, Building 36, Room 5D06, Bethesda, MD, 20205
Ann NY Acad Sci; 377:477-485 1981

Thymosin-alpha1 (alpha1) is a potent thymic polypeptide hormone. Using anti-alpha1 antibodies, we applied indirect immunofluorescence to human normal thymus of different ages and to hyperplastic, thymomatous, and 'involuted' thymus of myasthenia gravis (MG) patients. Alpha1 was localized only in the epithelial cells, lying singly, grouped, in Hassell's corpuscles, and proliferated in thymomas. Whereas normal thymuses had fewer and weakly stained cells, MG thymuses had many strongly positive epithelial cells; this was more evident in thymomas. Germinal centers were unstained. 'Involuted' MG thymuses had small islands of brightly stained cells lying among the fatty tissue. In cultured thymuses from three MG patients, epithelial cells but not fibroblasts were brightly stained for alpha1. Our findings (a) demonstrate the location. and presumably the origin, of alpha1 to be the thymic epithelial cell; (b) suggest the possibility that excess alpha1, because of its known effect on T-lymphocyte maturation and transformation of precursors to helper T-cells, may act pathologically to facilitate and perpetuate the dysimmune mechanism in MG; (c) may partially explain the beneficial effect of thymectomy in MG patients of any age; and (d) indicate that epithelial cells may be autonomous for the production of alpha1 as evidenced by their alpha1-positivity in culture. (Author abstract) (36 Refs)

28. INDUCTION AND AUGMENTATION OF MITOGEN-INDUCED IMMUNE INTERFERON PRODUCTION IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES BY NALPHA-DESACETYLTHYMOSIN ALPHA1.

Svedersky LP, Hui A, May L, McKay P, Stebbing N
Genentech Inc., 460 Point San Bruno Blvd., South San Francisco, CA, 94080
Eur J Immunol; 12(3):244-247 1982

Treatment of human peripheral blood lymphocytes with cloned Nalpha-desacetylthymosin alpha1 induced interferon production. The kinetics is similar to that of mitogen-induced interferon induction. Nalpha-desacetylthymosin alpha1, in combination with mitogen, augments the amount of interferon produced. This interferon is immune interferon (IFN-gamma) as determined by sensitivity to pH 2, lack of neutralization by antibodies to IFN-alpha or IFN-beta and absence of activity on MDBK cells. Although the mechanism of induction of IFN-gamma by Nalpha-desacetylthymosin alpha1 is unclear, this compound is not mitogenic at concentrations causing IFN-gamma production. These results indicate that thymic factors may also participate in the regulation of IFN-gamma production. (Author abstract) (25 Refs)

ADOPTIVE IMMUNIZATION AND RELATED APPROACHES

29. INTRACEREBRAL ADOPTIVE IMMUNOTHERAPY OF A MURINE LYMPHOMA ANTIGENICALLY ALTERED BY DRUG TREATMENT IN VIVO.

Romani L, Fioretti MC, Bianchi R, Nardelli B, Bonmassar E
Inst. Pharmacology, Univ. Perugia, Via del Giochetto, Perugia 06100, Italy
JNCI; 68(5):817-822 1982

Intracerebral tumor neutralization assay and adoptive immunotherapy with in vitro sensitized lymphocytes were done in immunodepressed mice challenged intracerebrally with L5178Y/DTIC lymphoma, a tumor subline antigenically altered by treatment with 5-(3,3-dimethyl-1-triazenyl)-1H-imidazole-4-carboxamide (DTIC) in vivo. Primary cytotoxic T-lymphocytes (CTL) were generated in vitro against L5178Y/DTIC cells with the use of splenocytes of histocompatible (BALB/cCr x DBA/2Cr)F1 donors. The extent of antitumor activity of CTL was evaluated by the measurement of tumor cell proliferation in the brain, as judged by the 125I-labeled 2'-deoxyuridine uptake values and by survival times of recipient mice. The results of the experiments showed: (a) CTL were highly effective in inhibiting tumor growth when they were injected along with L5178Y/DTIC tumor cells in a Winn-type neutralization assay; (b) the tumor inhibition mediated by CTL was specific, since no antilymphoma effects were detected when CTL sensitized against L5178Y/DTIC line were admixed with the parental L5178Y tumor or with other unrelated lymphoma cells; and (c) local adoptive immunotherapy with CTL given on Day 1,3, or 5 after the intracerebral challenge with L5178Y/DTIC lymphoma substantially impaired tumor cell proliferation and significantly increased survival times of recipient leukemic mice. (Author abstract) (37 Refs)

30. CULTURED HUMAN T-CELL LINES KILL AUTOLOGOUS SOLID TUMOURS.

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Dept. Immunology, Paterson Laboratories, Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England

Immunol Lett; 3(4):237-241 1981

An investigation concerning the possibility that the cytolytic activity of autoreactive T-cells, present in various lymphocyte preparations from cancer patients, might be amplified by expansion of the relevant subpopulations in T-cell growth factor (TCGF; Interleukin 2), is presented. Lymphocytes from peripheral blood, lymph node, spleen and tumor of seven patients with various carcinomas (2 lung, 3 colon, 1 stomach) and a parotid tumor, were cultured for 15 days in conditioned media containing TCGF. Cytotoxic activity was then determined against autologous tumor (and some autologous normal) cells and allogeneic tumor targets as evaluated in a short-term 51Cr-release assay. Significant cytotoxicity was detected in at least one effector preparation from all patients. This result was obtained under conditions where, in some cases, other autologous cells (normal lung, phytohemagglutinin-transformed lymphocytes) were resistant. The cytotoxicity also generally extended to allogeneic tumor targets, but lysis of K562, a cell line sensitive to natural killing, occurred in only 3/19 effector cell preparations. The results represent the first demonstration of cytotoxicity in human cultured T-cells (CTC) directed against autologous solid human tumor cells. The data are consistent with a polyclonal expansion of CTC of tumor-bearing patients which includes the amplification of a population recognitive of antigens expressed on autologous neoplastic cells. (19 Refs)

31. ALLOGENEIC BONE MARROW TRANSPLANTATION FOR ACUTE LEUKEMIA REFRACTORY TO INDUCTION CHEMOTHERAPY.

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Bone Marrow Transplantation Team, Univ. Texas M.D. Anderson Hosp., Houston, TX

Cancer Bull; 34(1):40-42 1982

Successful allogeneic bone marrow transplantation for primary refractory acute leukemia is described in a 20-yr-old white male. The effectiveness of total-body irradiation combined with an allogeneic bone marrow transplant is confirmed. Piperazinedione and fractionated total-body irradiation were used as cytoreductive treatment; good antileukemic efficacy compared to cytoxan and total-body irradiation was demonstrated. Low-dose methotrexate [15 mg/square meter (m2) on day 1; 10 mg/m2 on days 3, 7, and 11; weekly thereafter] was given as prophylaxis against graft-vs-host disease, which manifested itself 20 days after transplantation and again more definitely 16 mo after transplantation, with scleroderma-like involvement of the soft tissue of all extremities. Over the following 6 mo, a gradual response to immunosuppressive cyclophosphamide and prednisone was observed. (9 Refs)

SEROTHERAPY AND RELATED APPROACHES

32. CHARACTERIZATION OF A MONOCLONAL ANTIBODY REACTIVE WITH A SUBSET OF HUMAN BREAST TUMORS.

Yuan D, Hendler FJ, Vitetta ES

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JNCI; 68(5):719-728 1982

Fusion of spleen cells, from mice immunized against the human hormone-dependent breast cancer cell line ZR-75-1, with murine myeloma cells resulted in the establishment of a hybridoma cell line, HY59-H10(H59). The purified monoclonal IgM produced by the hybridoma reacts with the most differentiated human breast tumor cell lines but not with cells derived from normal breast secretions or with numerous other malignant cell lines. Of 106 biopsy specimens examined, H59 bound to 54% of malignant breast specimens, to 83% of fibroadenomas, and to 82% of specimens containing fibrocystic disease. Binding could not be detected in uninvolved breast tissue. (Author abstract) (52 Refs)

33. TUMOUR LOCALIZATION OF MONOCLONAL ANTIBODY AGAINST A RAT MAMMARY CARCINOMA AND SUPPRESSION OF TUMOUR GROWTH WITH ADRIAMYCIN-ANTIBODY CONJUGATES.

Pimm MV, Jones JA, Price MR, Middle JG, Embleton MJ, Baldwin RW

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Cancer Immunol Immunother; 12(2):125-134 1982

The tumor-localizing potential of Sp4/A4 monoclonal antibody to the rat mammary carcinoma Sp4 isolated from hybridoma supernatants was established and the therapeutic effectiveness of the monoclonal antibody conjugated to the broad-spectrum anti-tumor agent adriamycin (ADR) was assessed. Characterization of SP4/A4 is described. Following iv injection of 125I-Sp4/A4 antibody into normal WAB/Not rats, blood levels of the antibody dropped to 50% over the first 5 hr and then decreased more slowly, with a half-life of 40 hr. Urinary excretion averaged 18% of injected dose over the first 24 hr and showed similar rates over the next 3 days. Raised levels of Sp4/A4 were found in tumor tissue of rats with sc growths of SP4 as compared with lung, liver, spleen, kidney, and heart. The time course of 125I-Sp4/A4 uptake was examined. When rats bearing other tumors were included, levels of radioactivity in Sp4 tumor growths exceeded those in any of the organs examined, and the activity in other tumors was comparable to that in visceral organs. No preferential localization of 125-I-labelled normal rat immunoglobulin was observed in Sp4 tumors. Treatment of Sp4 tumor cells with Sp4-A4 antibody did not inhibit their growth in syngeneic rats; treatment of hosts with antibody similarly had no inhibitory effect on growth of an sc tumor challenge. Treatment of Sp4 cells with ADR-monoclonal antibody conjugates significantly retarded Sp4 tumor growth. The results indicated that monoclonal antibody directed against tumor cell surface antigens may be highly effective for tumor targeting of therapeutic agents. (22 Refs)

34. TISSUE DISTRIBUTION AND MOLECULAR PROFILE OF A DIFFERENTIATION ANTIGEN DETECTED BY A MONOCLONAL ANTIBODY (345.134S) PRODUCED AGAINST HUMAN MELANOMA CELLS.

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Cancer Immunol Immunother; 12(2):159-166 1982

The mouse IgG2a monoclonal antibody (MoAb) 345.134S secreted by a hybridoma derived from a mouse immunized with cultured human melanoma cells was examined in relation to the structure of the target antigen, the distribution of the antigen in normal and malignant tissues, and the expression of the antigen on cultured cells and its ability to function as a target of immune lysis. The structure detected by the MoAb 345.134S is composed of an 85 kilodalton (KD) glycopolypeptide linked by disulfide bridges with a 30 KD polypeptide carrying little or no carbohydrate. The 115 KD antigen appears to be peripheral rather than integral to the plasma membrane. Indirect immunofluorescence studies showed that the reactivity pattern of normal tissues with MoAb 345.134S does not correlate with their embryological origin. The majority of normal tissues gave only weak staining with MoAb 345.134S. All the types of tumors tested, except liver adenocarcinomas, reacted strongly with MoAb 345.134S, although there were some cases within each tumor group that were negative. MoAb 345.134S reacted in a radioimmunometric assay with a variety of cell lines, including melanoma, carcinoma, and lymphoid types. There was no relationship between the level of expression of the antigenic determinant recognized by MoAb 345.134S and other surface markers tested. The level of antigen detected by MoAb 345.134S was unchanged in the presence of interferon but was decreased by puromycin exposure. The opposite was true for cell-dependent lysis of cultured human cells. (32 Refs)

35. GD3, A PROMINENT GANGLIOSIDE OF HUMAN MELANOMA. DETECTION AND CHARACTERIZATION BY MOUSE MONOCLONAL ANTIBODY.

Pukel CS, Lloyd KO, Travassos LR, Dippold WG, Oettgen HF, Old LJ
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Exp Med; 155(4):1133-1147 1982

Mouse monoclonal antibody AbR24 has a high degree of specificity for human melanoma cells when tested on viable cell cultures. The protein A mixed hemagglutinin serological assay demonstrated an antigen detected AbR24, shown to be GD3 ganglioside by compositional and partial structural analysis and by comparison with authentic GD3 in thin layer chromatography. AbR24 reacted with authentic GD3 but not with any of the other standard gangliosides tested. Melanomas have a characteristic pattern of gangliosides; in all lines examined, glycolipids comigrating with GD3 and GM3 were prominent acidic glycolipids, with GD3 being the major component in many of the lines. GD3 was also prominent in extracts of mouse eye and bovine choroid. The only other line that had GD3 as the major component was MOLT-4 (a T cell line). Compared with 7% in the adult human brain, 9% in a renal cancer cell line, 11% in RAJI cells, and 33% in MOLT-4 cells, GD3 constituted 18-63% of the total ganglioside fraction in the melanoma cell lines. The 125I-protein A mixed hemagglutinin serological assay detected GD3 in all the cells and tissues examined. The apparent discrepancy between the ubiquitous presence of GD3 and the serological specificity of AbR24 for melanoma cells was explained by the localization and concentrations of GD3 in different cells. (31 Refs)

36. FIVE MELANOMA-ASSOCIATED ANTIGENS IDENTIFIED BY MONOCLONAL ANTIBODIES.

Hellstrom KE, Hellstrom I, Brown JP, Yeh MY, Woodbury RG
Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104
Protides Biol Fluid Proc Colloq; 29:877-882 1982

Mice were immunized with human melanomas and hybridomas were established that identify cell surface antigens. Five antigens were identified by monoclonal antibodies: antigens 3.1, p97, p155, p210, and 4.2. These antigens are described with respect to antibody, molecular nature, and specificity in cultured cells and biopsies. Antigen 3.1 is thought to be a glycolipid and exhibits specificity for a small subgroup of cultured melanomas and biopsy material from melanomas and normal tissues. Antigen p97 is a 97,000 mol wt glycoprotein with specificity for approx 50% of cultured melanomas and biopsy tissue from approx 50% of biopsied melanomas and some fetal tissues. Antigen p155 is a 155,000 mol wt protein (possibly a glycoprotein) and exhibits specificity in cultured and biopsied melanomas. Antigen p210 is a 210,000 mol wt protein (possibly a glycoprotein) exhibiting specificity in approx 30% of cultured melanomas and 25% cultures of other tumors and in biopsies of melanomas, other tumors, and adult and fetal brain. Antigen 4.2 may be a glycolipid and exhibits specificity for approx 80% of cultured melanomas and a few other tumors. The implications of these findings in diagnosis and therapy of human melanomas and other tumors are discussed. (24 Refs)

37. MOLECULAR HETEROGENEITY OF A HIGH MOLECULAR WEIGHT HUMAN MELANOMA ASSOCIATED ANTIGEN DETECTED BY MONOCLONAL ANTIBODIES.

Imai K, Wilson BS, Ruberto G, Nakanishi T, Yachi A, Ferrone S
Dept. Molecular Immunology, Scripps Clinic and Res. Foundation, La Jolla, CA
Protides Biol Fluid Proc Colloq; 29:893-897 1982

The spatial relationship among antigenic determinants recognized by four monoclonal antibodies (MoAbs) specific for a human high mol wt melanoma-associated antigen (MAA) was analyzed. The four MoAbs were compared in direct and indirect inhibition binding assays to determine whether they identified the same or different antigenic determinants. MoAbs 138.13S, 225.28S, and 653.40S recognized the same or closely associated antigenic determinants which were distinct from that recognized by MoAb 763.24T. Sequential immunodepletion studies demonstrated that the high mol wt MAA may be divided into three subpopulations: Group 1 carries the antigenic determinants recognized by the MoAb 138.13S (225.28S or 653.40S) and 763.24T; Group 2 carries only the determinants recognized by MoAb 138.13S (225.28S or 653.40S); and Group 3 carries only the determinants recognized by the MoAb 763.24T. The amount of high mol wt molecules in each subpopulation was in the order of Group 1 greater than Group 2 greater than Group 3. (7 Refs)

38. REACTIONS OF MONOCLONAL ANTIBODIES AGAINST HUMAN MELANOMA WITH DIFFERENT TISSUES AND CELL LINES.

Hageman P, Vennegoor C, Van der Valk M, Landegent J, Jonker A, Van der Mispel L.

Div. Clinical Oncology, The Netherlands Cancer Inst., Amsterdam, The Netherlands

Protides Biol Fluid Proc Colloq; 29:889-892 1982

Spleen cells from a BALB/c mouse immunized with plasma membrane from the human melanoma cell line MeWo were fused with the IgG-1 producing mouse myeloma cell line P3X63Ag8. Antibodies from seven hybridomas were tested for their reactions on various cell lines and tissues. The antibodies reacted with many melanoma cell lines but did not show high specificity in the 125I-F(ab')2 anti-mouse IgG binding assay; they reacted with a number of control tumor and normal cell lines. Sera were tested with an immunoperoxidase sandwich test on thin sections of frozen tissue from melanoma metastases; mammary tumors; normal skin, brain, lung and mammary gland; fetal tissues; and mammary tissues of dog, cat and mouse. Four distribution patterns were observed: one hybridoma produced antibodies with a broad tissue distribution and the reaction was directed against an 88,000 dalton protein; two groups of antibodies reacted primarily with metastatic melanomas; and one antibody reacted with melanoma and other tissues, particularly human mammary tumor. (8 Refs)

39. ANTIGEN EXPRESSION AND IMMUNE LYSIS OF HUMAN MELANOMA CELLS: ANALYSIS WITH MONOCLONAL ANTIBODIES.

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Dept. Internal Medicine, Sapporo Medical Coll., Sapporo, Japan

Protides Biol Fluid Proc Colloq; 29:883-888 1982

The complement dependent and cell dependent lysis of cultured human melanoma cells (line Colo38) sensitized with monoclonal xenoantibodies to tumor-associated antigens and to normal surface markers was investigated. The relationship between the increase in the number of antigen-antibody interactions on cell membrane and extent of immune lysis was studied. A significant difference in the ability of monoclonal antibodies to human melanoma-associated antigens, to HLA-A,B antigens, to Ia-like antigens, and to a membrane-bound glycoprotein with an apparent mol wt of 85,000 daltons to mediate cell dependent and complement dependent lysis of the Colo38 was observed. No relationship was found between the lytic efficiency of the antibodies and the level of expression of the corresponding determinants on the cell membrane. While sensitization of target cells with combinations of antibodies increased the number of antigen-antibody interactions on the cell membrane, no significant change was observed in the extent of lysis of target cells. Human complement did not affect lysis of melanoma cells, even when they were sensitized with combinations of monoclonal antibodies to the markers tested. Augmentation of HLA-A,B antigens on interferon-treated melanoma cells was associated with an increase in the extent of immune lysis mediated by the corresponding antibodies. Since the relationship between changes in antigen density and extent of immune lysis is not a general phenomenon, the conflicting results in the literature on the role of antigen density in immune lysis can be explained. (9 Refs)

40. TUMOR-ASSOCIATED NEURAL DIFFERENTIATION ANTIGENS DETECTED ON C1300 NEUROBLASTOMA CELLS BY HYBRIDOMA MONOCLONAL AUTOANTIBODIES.

Revoltella RP, Businaro R, Lauro G, Toesca A

Lab. Cell Biology, CNR, Via G. Romagnosi 18/A, 00196 Rome, Italy

Cell Immunol; 68(1):75-92 1982

Immune isoantisera and hybridoma monoclonal autoantibodies against syngeneic C1300 neuroblastoma (NB) cells were produced from BALB/c mice. Isoantisera were obtained (i) from mice immunized with membrane preparations from cloned NB cells and (ii) from mice bearing NB tumors. After repetitive absorptions on several different syngeneic or allogeneic tumor cell lines and syngeneic normal kidney, liver, spleen, bone marrow, and brain mouse tissue powders, these sera still retained antibodies reacting with tissue-differentiation antigens present on both NB cells and normal nerve sympathetic cells on cryostat whole body sections of neonatal mice. Monoclonal autoantibodies against NB cells were the products of the fusion between plasmacytoma cells and spleen cells from mice bearing syngeneic NB tumors. These anti-NB monoclonal antibodies revealed a restricted spectrum of distinct alloantigenic specificities against syngeneic bone marrow, fetal and adult brain cells, and nerve sympathetic cells present on neonatal rather than adult mice. A mixture of four monoclonal antibodies, recognizing, respectively, an epitope of the Ia complex and three distinctive neuronal-restricted antigens, proved to be a powerful and specific probe for histological immunodiagnosis of neuroblastoma, on cryostat sections of NB tumors, metastases, and tumor-draining lymph nodes. (Author abstract) (34 Refs)

41. MONOCLONAL ANTIBODIES AGAINST HUMAN THYMOCYTES AND T LYMPHOCYTES.

Tax WJ, Willems HW, Kibbelaar MD, De Groot J, Capel PJ, De Waal RM, Reekers P, Koene RA

Dept. Nephrology, St. Rabdoudziekenhuis, Nijmegen, The Netherlands

Protides Biol Fluid Proc Colloq; 29:701-704 1982

The specificity of two cytotoxic monoclonal antibodies (WT 1 and WT 2) produced by the hybridoma technique was analyzed by cytotoxicity, indirect immunofluorescence, and the enzyme-linked immunosorbent assay WT 1 was reactive with all human thymocytes and all peripheral T lymphocytes, but did not react with any other cell type from peripheral blood. WT 1 also bound to phytohemagglutinin (PHA)-stimulated T cells and to cytotoxic T lymphocytes induced by mixed lymphocyte culture. Monkey lymphocytes also reacted with WT 1 and therefore functional aspects of this antibody, such as immunosuppressive activity, can be studied in the monkey. WT 1 was not mitogenic and did not interfere with PHA stimulation. WT 1 did not block formation of erythrocyte-rosettes and appeared to be unreactive with myeloid progenitor cells. On the other hand, the growth of myeloid colonies was inhibited by prior incubation of bone marrow cells with rabbit complement and monoclonal antibody WT 2. WT 2 was not reactive with peripheral granulocytes or monocytes, and bound to all thymocytes and a small percentage of peripheral lymphocytes. (10 Refs)

42. A MONOCLONAL ANTIBODY DEFINING A BURKITT LYMPHOMA ASSOCIATED ANTIGEN.

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Protides Biol Fluid Proc Colloq; 29:899-902 1982

Reactivity of monoclonal antibody 38-13, obtained by fusing murine myeloma cells with Lewis rat splenocytes sensitized with Daudi cells (human Burkitt lymphoma), was investigated. Negative results were obtained in all patients with B chronic lymphoid leukemia, acute lymphoid leukemia (T and nonT-nonB), acute myeloid leukemia, acute monoblastic leukemia, Hodgkin's disease, T cell lymphosarcoma, and B cell lymphosarcoma (nodular and diffuse). Positive results were observed in 4/8 patients with B cell Burkitt lymphoma. When the specific reactivity of 38.13 ascites was tested with a panel of cell lines of various origins, both by complement dependent lymphocytotoxicity tests and indirect membrane immunofluorescence assays, all the positive target cells were of Burkitt's lymphoma origin. Negative results were obtained with 15 Epstein-Barr virus positive lymphoblastoid cell lines, 4 T cell lines, a chronic myelogenous leukemia cell line, 4 teratoma cell lines, and one each of melanoma and neuroblastoma. The 38.13 monoclonal antibody may be useful for diagnosis and specific immunotherapy of Burkitt lymphomas. (8 Refs)

43. PREPARATION AND CHARACTERIZATION OF MONOCLONAL ANTIBODIES AGAINST ANTIGENS OF HUMAN RENAL ADENOCARCINOMA.

Hess H, Alheid U, Biermann S, Waks T, Scherberich JE, Mondorf AW, Schoeppe W, Senge T, Falkenberg FW
Dept. Nephrology, Center for Internal Medicine, Klinikum J. W. Goethe Universitat, 6000 Frankfurt am Main, W. Germany
Protides Biol Fluid Proc Colloq; 29:903-905 1982

Lymphocytes from BALB/c mice hyperimmunized by four and eight consecutive injections of renal adenocarcinoma plasma membranes were fused with X63-Ag 8.653 plasmacytoma cells. In the supernatants of 90/600 wells with viable cells, antibodies reactive with antigens in tumor and/or kidney were found. Twenty-two clones were isolated and characterized. Tumor cell membranes, capillaries and intercellular matrix were recognized by the various monoclonal antibodies. Generally, the density of antigenic determinants was higher in the tumor than in normal kidney tissue. No monoclonal antibodies were found that reacted exclusively with tumor. Localization of antigenic determinants in the kidney was easy, while in the tumor tissue localization could not be defined exactly. Antibodies of Hyp I 164 D5 and Hyp I 289 A1 reacted with tumor cell membranes, antibody Hyp I 238 A9 with capillaries. (5 Refs)

44. HUMAN-MOUSE HYBRIDOMA CELLS PRODUCING ANTIBODIES.

Astaldi GC, Willems C, Alleyne W, Lansdorp P, Zeijlemaker WP, Janssen M
Central Lab., Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands
Protides Biol Fluid Proc Colloq; 29:609-614 1982

Xenogeneic hybridomas between human lymphocytes and mouse myeloma cells were produced and the effects of various factors on their growth were studied. After fusion, cells were resuspended in culture medium containing 10% human endothelial culture supernatant (HECS) and when hybrid clones developed, the supernatants were tested for the presence of antibodies against RhD+ RBC. The hybridoma cells producing anti-D activity were expanded and cloned by limiting dilution in culture medium containing 10% HECS. Six days of culture in the presence of pokeweed mitogen strongly increased the yield of hybridoma cells. The recovery of hybridoma cells producing anti-D antibodies was significantly increased by culturing the lymphocytes in the presence of RhD+ RBC together with endothelial cells. All eight hybridoma supernatants agglutinating RhD+ RBC had specificity for the D antigen. Specific antibody production decreased markedly with time, indicating the instability of the xenogeneic hybridoma cells. Selection for antibody-producing clones was accomplished by culturing at low density and discarding negative clones. The percentage of wells containing hybridoma cells producing anti-D antibodies increased upon each passage up to the fourth passage, when a plateau was reached. Thus, when lymphocytes obtained from persons who had been immunized with allogeneic RhD+ RBC were fused with mouse myeloma cells, hybridoma cells were obtained producing specific anti-D antibodies. (13 Refs)

45. SPECIFIC KILLING OF HUMAN AND MOUSE TUMOR CELLS BY IMMUNOTOXINS.

Casellas P, Blythman HE, Brown JP, Gros O, Gros P, Hellstrom KE, Hellstrom I, Jansen FK, Poncelet P, Vidal H
Centre de Recherches CLIN MIDY, Monpellier, France
Protides Biol Fluid Proc Colloq; 29:927-932 1982

Monoclonal antibodies (anti-Thy 1.2 and anti-human melanoma P97) were used to replace the binding moiety of the B-chain of ricin, in order to obtain immunotoxins that use the purified A-chain of ricin as the toxic moiety. The A-chain was coupled to the antibodies via a disulfide linkage, allowing a linkage of active A-chain to antibody ratio of 3:1 for IgM anti-Thy 1.2 and 1.4:1 for the IgG anti-melanoma immunotoxin. Both immunotoxins showed specific cytotoxicity for their respective target cells. In vitro tests of protein synthesis inhibition and of inhibition of colony formation demonstrated the specific activity of the immunotoxins. Both immunotoxins could specifically kill the last target cell without damaging control cells, and a specific killing index could be calculated. The loss of binding capacity due to conjugation was estimated to be 10% for anti-Thy 1.2 immunotoxin and 30% for anti-melanoma immunotoxin. (11 Refs)

46. THE POTENTIAL USE OF MONOCLONAL ANTIBODIES IN DRUG TARGETING.

Rowland GF, Simmonds RG, Corvalan JR, Marsden CH, Johnson JR, Woodhouse CS, Ford CH, Newman CE
Lilly Res. Centre, Erl Wood Manor, Windlesham, Surrey, England
Protides Biol Fluid Proc Colloq; 29:921-926 1982

Conjugates of vindesine (VDS) and polyclonal antibodies were prepared. In vitro targeting was demonstrated with an indirect or 'sandwich' technique. VDS-goat anti-rabbit conjugates were used with either mouse T lymphoma cells (EL4) or human anaplastic lung tumor cells (CALU-6). Cells were exposed to appropriate rabbit antiserum for 30 min, unbound antibody was washed away, and the cells were further incubated with VDS-goat anti-rabbit antibody. The number of EL4 cells increased during the first 24 hr of growth following such treatment. Similar results were obtained with CALU-6 cells following 2 hr of incubation. Cytostatic effects were obtained in both cell types only when the VDS conjugate could recognize the first layer antibody as a target. When VDS-sheep anti-carcinoembryonic antigen (CEA) IgG was used, the VDS-antibody conjugate was more cytotoxic than free VDS, mixtures of VDS and antibody, or a conjugate of VDS and normal sheep IgG. Approx 25x less conjugated VDS was necessary than free VDS to kill 50% of the cells. Several fusions were attempted in order to produce specific monoclonal anti-CEA antibodies; a high yield of active hybridomas was achieved. (10 Refs)

47. DRUG TARGETING WITH MONOCLONAL ANTIBODIES.

Page M, Emond JP, Gauthier C, Dufour C, Innes L
Dept. Biochemistry, Universite Laval, Quebec, Canada
Protides Biol Fluid Proc Colloq; 29:933-936 1982

Conjugates of daunomycin (DAU) with anti-carcinoembryonic antigen (CEA) were prepared by covalently binding DAU to monoclonal antibodies with 0.01% glutaraldehyde. The pharmacological activity of the conjugate was assayed in vitro with human colon adenocarcinoma cells producing CEA (Lovo cells). At a drug:protein ratio of 5.7, the inhibition of thymidine incorporation was measured at various concentrations. At 500 nanog/ml, the DAU monoclonal anti-CEA conjugate was 8x more active than free DAU. The total inhibition of thymidine incorporation was only slightly better than that for free DAU when DAU plus monoclonal antibody were used. Free monoclonal anti-CEA did not affect thymidine incorporation. Compared with 0.1, 0.2, and 0.5 ug/ml of free DAU, inhibition of thymidine incorporation by the conjugate was increased by at least 2x. These results demonstrate that monoclonal conjugates retain both their pharmacological and immunological activity and that monoclonal anti-CEA can be a drug carrier for cancer treatment. (8 Refs)

CLINICAL IMMUNOLOGY

48. COMPARISON OF THE TECHNIQUES USED FOR MONITORING HUMORAL IMMUNITY IN CANCER PATIENTS.

Renk CM, Gupta RK, Irie RF, Morton DL
Dept. Surgery, Medical Coll. Ohio, Toledo, OH, 43699
J Surg Oncol; 19(3):155-161 1982

The humoral immune response to tumor-associated antigens (TAA) in cancer patients undergoing immunotherapy can vary considerably. This variability is inherent from patient to patient and is also dependent on the type of assay used to measure patient antibody response to tumors. In this investigation four serological techniques, complement-dependent antibody-mediated cytotoxicity, immune adherence, complement fixation, and indirect membrane immunofluorescence, were used to assess the humoral immune response in melanoma patients receiving specific immunization with cultured allogeneic melanoma cell vaccine. Two different patterns of antibody response were elicited. One was directed against TAA and oncofetal antigens (OFA) and the other was against HLA antigens. The sensitivity and reactivity varied among the different techniques suggesting that one test or technique may not be sufficient to evaluate critically a patient's response to immunotherapy. (Author abstract) (18 Refs)

49. COMPARISON OF EFFECTS OF LEUKOCYTE AND FIBROBLAST INTERFERON ON IMMUNOLOGICAL PARAMETERS IN CANCER PATIENTS.

Lucero MA, Magdelenat H, Fridman WF, Pouillart P, Billardon C, Billiau A, Cantell K, Falcoff E
(c/o Billiau), Rega Inst. Medical Res., Minderbroedersstraat 10, B-3000 Leuven, Belgium
Eur J Cancer Clin Oncol; 18(3):243-251 1982

Patients with metastastic cancer were given single intramuscular injections of 10(7) units of partially purified preparations of either leukocyte or fibroblast IFN. Serum levels of interferon, of beta2-microglobulin and of carcino-embryonic antigen (CEA), as well as NK activity of circulating lymphocytes, were followed over a period of 96 hr post injection. In confirmation of previous studies, levels of circulating IFN were lower after injection of fibroblast IFN than after injection of leukocyte IFN. Despite this difference in pharmacokinetics, the natural killer activity of circulating lymphocytes was enhanced with both IFNs. Levels of CEA were not influenced by the IFN injections. Leukocyte but not fibroblast IFN caused an increase in serum levels of beta2-microglobulin in the circulation. A similar difference between leukocyte and fibroblast IFN in their ability to influence the beta2-microglobulin system was observed in experiments on cell cultures. Only leukocyte IFN was able to cause release of beta2-microglobulin by either leukocytes or fibroblasts. (Author abstract) (32 Refs)

50. MODULATION OF NATURAL KILLER CELL-MEDIATED CYTOTOXICITY BY PARTIALLY PURIFIED AND CLONED INTERFERON-ALPHA.

Lotzova E, Savary CA, Gutterman JU, Hersh EM
Dept. Clinical Immunology and Biological Therapy, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Res; 42(6):2480-2488 1982

We have studied peripheral blood of 35 normal individuals, 28 solid-cancer patients, and 14 leukemic patients for natural killer (NK) cell cytotoxicity to K-562 and CEM tumor cells in a 51Cr release cytotoxicity assay. We have found that both normal individuals and solid-cancer patients could be grouped into high (NK-HR), medium (NK-MR), and low (NK-LR) NK cell responder categories with regard to their degree of NK cell activities. However, in general, NK-HRs were found to be prevalent in normal donor population and NK-LRs in cancer patients. Leukemic patients always exhibited the NK-LR status. The difference between NK-HRs and NK-MRs appeared to be due to the relative decrease in number of active NK cells. In contrast, the NK-LR status could not be contributed to decrease of NK cells because of the dichotomy in NK cell dose-response patterns of NK-LRs versus those of NK-HRs and NK-MRs. Eighteen cancer patients undergoing interferon-alpha (IFN-alpha) therapy (3 x 10(6) units, im, daily) were also tested for NK cell activities after single or multiple IFN-alpha injections. There was a highly significant and consistent increase in NK cell cytotoxicity of patients with the NK-LR and NK-MR phenotypes following one injection of IFN-alpha. In contrast to the NK-LR and NK-MR group of patients, most patients displaying the NK-HR phenotype failed to show any NK cell augmentation following any number of IFN-alpha injections (up to 119). We have also tested NK cell activities of cancer patients undergoing treatment with low (3 x 10(6) units) and high (36 x 10(6) and 50 x 10(6) units) doses of clone A of recombinant IFN-alpha (IFN-alpha rA). In these studies, all patients receiving the lower doses of IFN-alpha rA and three of five patients receiving the higher doses of IFN-alpha rA displayed augmented Nk cell activity 24 hr after a single im injection. Analysis of patients receiving the low dose of IFN-alpha rA in a single-cell assay suggested that this agent did not modulate tumor-NK cell-binding properties but augmented significantly Nk cell cytotoxicity and killing of already-bound tumor targets. (Author abstract) (50 Refs)

51. CYTOTOXIC ANTIBODY REACTIVITY IN SERA OF MELANOMA PATIENTS AGAINST ALLOGENEIC AND AUTOLOGOUS CULTURED TUMOR CELLS AND FIBROBLASTS.

Brown JM, Shoffner PC, Tondreau SP, Matthews EJ, Terry WD, Rosenberg SA
Div. Surgical Oncology, Univ. Illinois Medical Center, 840 South Wood, Chicago, IL, 60612
Cancer Res; 42(6):2216-2222 1982

Using a complement-dependent microcytotoxicity assay, sera from melanoma patients were analyzed for antibody reactivity with cultured melanoma and normal adult skin fibroblasts. Sera from Stage I tumor-bearing patients prior to surgical excision, poor-prognosis Stage I and Stage II patients after tumor excision and lymphadenectomy but prior to adjuvant therapy, and normal individuals with a similar age and sex distribution were tested against a melanoma-fibroblast pair from an allogeneic donor. The groups displayed a wide range of cytotoxicity against both cell types, and no serum possessed melanoma-specific reactivity. Mean cytotoxicity of the Stage I tumor-bearing group was not significantly different (p greater than 0.05) from that of the normal group for either target cell, and patients whose tumors went on to recur were not different from nonrecurrent patients. The Stage I and II postlymphadenectomy patients were not different from the normals in fibroblast reactivity. However, melanoma reactivity was significantly higher in the postlymphadenectomy patients than the normals (p less than 0.02). This was the result of an elevated reactivity in the patient population who remained disease free compared to patients whose tumors went on to recur (p less than 0.01), although a large overlap existed between these two groups. Cytotoxicity against autologous melanoma and fibroblasts was observed with sera obtained throughout the clinical course of four Stage II patients, and no melanoma-specific reactivity was detected. Absorption with cultured fetal fibroblasts of sera from Stage II patients both before and after immunotherapy with Bacillus Calmette-Guerin and allogeneic melanoma removed reactivity against allogeneic and autologous melanoma and adult fibroblasts. Therefore, the predominant antibody reactivity detected in these patients was directed against common fetal fibroblast-associated antigen, and no evidence was obtained for the presence of antibodies reactive with unique or shared tumor-specific antigens. (Author abstract) (35 Refs)

52. SYSTEMIC ADMINISTRATION OF HUMAN LEUKOCYTE INTERFERON TO MELANOMA PATIENTS. I. EFFECTS ON NATURAL KILLER FUNCTION AND CELL POPULATIONS.

Golub SH, Dorey F, Hara D, Morton DL, Burk MW
Div. Oncology, Dept. Surgery, Univ. California Los Angeles Sch. Medicine, Los Angeles, CA, 90024
JNCI; 68(5):703-710 1982

Natural killer (NK) cytotoxicty was assessed against K562 targets in 14 melanoma patients who received daily im doses of human leukocyte interferon (IFN) for 42 consecutive days. The most common pattern of NK activity was a decline from pretreatment levels 1 day after initiation of treatment, followed by increasing cytotoxicity with peak activity at Day 7 and a subsequent gradual decline to pretreatment levels during the remaining wk of treatment. This pattern was particularly apparent in patients who received 3 x 10(6) or 9 x 10(6) U IFN/day, while patients who received 1 x 10(6) U IFN/day tended to lack the decline at Day 1 and maintained the elevated NK activity past Day 7. Changes in NK activity could not be related to changes in absolute lymphocyte counts; to proportions of cells bearing membrane receptors for sheep RBC, of cells bearing membrane receptors for erythrocyte-antibody-complement, or of cells bearing FCgamma receptor, or to clinical response to IFN. (Author abstract) (23 Refs)

53. SYSTEMIC ADMINISTRATION OF HUMAN LEUKOCYTE INTERFERON TO MELANOMA PATIENTS. II. CELLULAR EVENTS ASSOCIATED WITH CHANGES IN NATURAL KILLER CYTOTOXICITY.

Golub SH, D'Amore P, Rainey M
Div. Oncology, Dept. Surgery, Univ. California Los Agneles Sch. Medicine, Los Angeles, CA, 90024
JNCI; 68(5):711-717 1982

Treatment of patients with malignant melanoma with daily doses of human leukocyte interferon (IFN) resulted in natural killer (NK) cytotoxicity that increased during the 1st week of treatment and subsequently declined to pretreatment levels despite continued IFN administration; events involved in these changes were examined. The increased cytotoxicity was associated with an increased number of cells able to bind K562 targets and an increased proportion of cells able to mediate cytolysis of K562 targets. The period of increasing NK activity was also associated with an increased ability to generate in vitro cytotoxic effectors against K562 targets by stimulation with allogeneic lymphoblastoid cells. The responding cells in this system were depleted of NK activity by adherence to immune complexes. These results suggested that increased NK activity during Week 1 of in vivo treatment was associated with augmentation of the development of NK cells from noncytotoxic precursors in addition to direct effects on NK cells. In contrast, the decline in NK activity appeared to be primarily a direct effect on NK cells, because these cells could no longer be augmented in vitro by additional IFN. The refractory state of IFN augmentation of cytotoxicity was limited to the period of IFN treatment in vivo, and responsiveness to IFN was promptly regained upon cessation of treatment. No evidence for the development of suppressor cells of NK effector function could be obtained. (Author abstract) (24 Refs)

54. PROTEIN A REACTIVITY OF LYMPHOCYTES FROM SOME PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA MEDIATED BY AN INTERACTION WITH THE F(AB')2 REGION OF SURFACE IMMUNOGLOBULIN.

Romagnani S, Giudizi MG, Biagiotti R, Almerigogna F, Del Prete GF, Maggi E, Ricci M
(c/o Ricci) Immunologia Clinica, Istituto Clinica Medica 3, Policlinico Careggi, 50134-Firenze, Italy
Scand J Immunol; 15(3):287-295 1982

Peripheral blood lymphocytes (PBL) from 15 of 38 patients with chronic lymphocytic leukemia (CLL) were capable of forming rosettes with human erythrocytes coated with staphylococcal protein A (SpA-HRBC). PBL from seven patients also showed a marked proliferative response after stimulation with Staphylococcus aureus bacteria strain Cowan I (Cowan Staph). The SpA-rosetting of CLL cells was inhibited by incubation with F(ab')2 fragments of anti-immunoglobulin (Ig) antibodies. In addition, incubation with these fragments inhibited the proliferative response of leukemic B cells to Cowan Staph. The Cowan-Staph-induced proliferation of CLL cells was also impaired by the addition of normal human IgG and human IgG F(ab')2 fragments to the cultures, whereas non-immune rabbit IgG was not inhibitory. The inhibitory activity of human IgG F(ab')2 fragments was retained by a SpA-Sepharose column, and it was found in the material recovered from the same column by acid elution. These data indicate that an interaction between SpA and a structure located in the F(ab')2 region of surface Ig of different classes is responsible for either SpA-binding or the Cowan-Staph-induced proliferative response of PBL from some patients with CLL. (Author abstract) (24 Refs)

55. IMMUNE COMPLEXES IN OVARIAN CANCER.

Clayton LA, Gall SA, Dawson JR, Creasman WT
Div. Gynecologic Oncology, Dept. Obstetrics and Gynecology, Duke Univ. Medical Center, Durham, NC, 27710
Gynecol Oncol; 13(2):203-212 1982

A polyethylene glycol precipitation (PEG) assay has been used to identify immune complexes in the serum of patients with ovarian cancer. Single radical immunodiffusion was used to quantitate the amount of IgG contained in the immune complexes. This study has shown that significantly higher levels of immune complexes were detected in the serum of ovarian cancer patients with known tumor when compared with ovarian cancer patients who were in remission. Values obtained for patients in remission were within the range of the control group. The levels of immune complexes were also noted to rise before the clinical detection of recurrences or progression of disease. It is therefore suggested that the PEG assay may be a useful marker in patients with ovarian cancer. (Author abstract) (25 Refs)

56. NATURAL KILLER CELL ACTIVITY IN GASTROINTESTINAL CANCER PATIENTS - DECLINE IN NATURAL KILLER CELL ACTIVITY IN TGAMMA CELLS AND THE ACTION OF INTERFERON ON ITS INCREASE.

Mugitani H, Suzuki M, Naruki Y, Ohtsuka S, Shinbo T
First Dept. Internal Medicine, Toho Univ. Sch. Medicine, Ota-ku, Tokyo, Japan
Nippon Gan Chiryo Gakkai Shi; 16(7):1371-1376 1981

Effects of interferon (IF) on natural killer (NK) cell activity of Tgamma-cells (IgG-Fc receptor-positive T cells) were investigated in peripheral blood lymphocytes of 21 patients with gastrointestinal cancer (17 gastric, 2 esophageal, 1 large intestine, and 1 gall bladder). T cells were isolated from peripheral blood lymphocytes, using the E-rosette sedimentation reaction; Tgamma-cells were isolated using theophylline. Release of 51Cr from 51Cr-labeled K562 cells was used to measure the NK cell activity. In 10 healthy subjects, the NK cell activity of mononucleocytes (MNC) was 46.5 +-13.1% and that of Tgamma-rich cells was 47.7 +-11.3%; these values were used as standards for NK cell activity in determinations of cytotoxic index. The cytotoxic index was applied to the NK cell activities of lymphocytes of the patients. The Tgamma cells showed a decline in NK cell activity in most of the 21 patients; there was also a decrease in NK cell activity in the MNC in these patients. Addition of 1,000 units of IF increased the NK cell activity of the MNC, T-rich and Tgamma-rich cells. The results suggested that the decreased NK cell activities of the Tgamma cells and the MNC may be due to decreased effector cell functioning and decreased production of IF. (27 Refs) (In JPN)

57. IMMUNOLOGIC CHARACTERIZATION OF A HELPER T-CELL LYMPHOMA.

Gramatzki M, Dolan MF, Fauci AS, Maples JA, Bonnard GD, Strong DM

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Blood; 59(4):702-708 1982

The lymphocytes of a patient with a T-cell non-Hodgkin's lymphoma with peripheral blood involvement and polyclonal hypergammaglobulinemia were characterized in terms of surface markers and immunologic functions. Using the fluorescence-activated cell sorter and employing various monoclonal antibodies against T-cell surface antigens, it was shown that almost all of the patient's peripheral blood lymphocytes were positive for OKT4 and 9.3, antibodies that recognize helper T-cell subset. The circulating lymphoma cells had typical characteristics for T cells; they formed spontaneous rosettes with sheep erythrocytes and stained with the pan T-cell antibodies 9.6 and 10.2, but did not react with other anti-T-cell monoclonal reagents such as OKT3, UCHT-1, and 3A1. The cells appeared to be mature by the fact that they did not stain with OKT6, and terminal deoxynucleotidyl transferase was undetectable. Functionally, they were able to provide 'help' for antibody production, and they could be stimulated to produce moderate amounts of interleukin-2, while unable to proliferate in response to mitogens. Morphologically, some of the lymphocytes showed a deeply cleaved nucleus. (Author abstract) (53 Refs)

58. IMMUNOLOGIC EVALUATION OF T CHRONIC LYMPHOCYTE LEUKEMIA CELLS: CORRELATIONS AMONG PHENOTYPE, FUNCTIONAL ACTIVITIES, AND MORPHOLOGY.

Pandolfi F, De Rossi G, Semenzato G, Quinti I, Ranucci A, De Sanctis G, Lopez M, Gasparotto G, Aiuti F

Dept. Clinical Immunology, Viale dell'Universita, 37, 00161 Rome, Italy

Blood; 59(4):688-695 1982

Chronic lymphocytic leukemia of T-cell origin (T-CLL), a rare variant of CLL, appears to be a clonal proliferation of mature T cells of one of several subsets. In the cells of seven T-CLL patients, surface markers (including those reacting with a panel of monoclonal antibodies), functional activities, and electron microscopic morphology were evaluated. The phenotypic patterns of circulating T-CLL cells correspond to those of normal mature T-cell subsets. The cells of three patients demonstrated at least one marker reported to be expressed by suppressor/cytotoxic T cells; those of three patients expressed markers apparently linked with T-helper activity. Cells from one patient appeared to be a heterogeneous proliferation of more than one T-cell subset. These T-Cll cells may also retain some of the functional activity of the normal T subpopulations. Our data indicate that a combination of several tests should be used to characterize the proliferating cells in T-CLL. (Author abstract) (29 Refs)

59. T-LYMPHOCYTE RECONSTITUTION IN RECIPIENTS OF BONE MARROW TRANSPLANTS WITH AND WITHOUT GVHD: IMBALANCES OF T-CELL SUBPOPULATIONS HAVING UNIQUE REGULATORY AND COGNITIVE FUNCTIONS.

Friedrich W, O'Reilly RJ, Koziner B, Gebhard DF, Good RA, Evans RL
(c/o Evans), Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 59(4):696-701 1982

The development of T lymphocytes in 34 patients engrafted with allogeneic bone marrow was studied by indirect immunofluorescence using mouse monoclonal antibodies. Two antibodies, termed anti-Leu-1 and anti-Leu-4, react with distinct membrane components expressed by all peripheral T cells, whereas two other antibodies, termed anti-Leu-2a and anti-Leu-3a, react with complementary subsets of Leu-1+ and Leu-4+ lymphocytes. The Leu-2a+3a- (Leu-2) subset contains suppressor/cytotoxic T cells, and the Leu-2a-3a+ (Leu-3) subset contains helper T cells. The ratio of Leu-2/Leu-3 T cells was elevated in nearly all patients studied during the 1st mo of engraftment, but this ratio subsequently returned to normal in patients with an uncomplicated course or with solved acute GVHD. In contrast, a deficiency of helper T cells with a resultant preponderance of suppressor/cytotoxic T cells persisted in all patients studied with both acute and chronic GVHD after the 1st mo. The implications of these findings in regard to the functions of these cells in vitro are discussed. (Author abstract) (23 Refs)

REVIEWS

60. IMMUNOTHERAPY OF MALIGNANT MELANOMA.

Thiers BH
Dept. Dermatology, Medical Univ. South Carolina, Charleston, SC
J Am Acad Dermatol; 6(4,part1):559-562 1982

A correlation between cutaneous reactivity of dinitrochlorobenzene (DNCB) and the stage of malignant melanoma (MM) has been found; in Stage II, a correlation between DNCB reactivity and prognosis has been found. Trials of immunotherapy in MM patients have included BCG, vaccines of irradiated, neuraminidase-treated autochthonous MM cells, levamisole (which increases cell-mediated immunity in immunodeficient patients), transfer factor, and interferon, often in combination with antitumor agents (usually dacarbazine). No form of immunotherapy has as yet shown consistent value in the treatment of Stage I-II MM, but the potential of this treatment is great. (44 Refs)

61. SPECIFIC AND NONSPECIFIC IMMUNOTHERAPY AS AN ADJUNCT TO CURATIVE SURGERY FOR CANCER OF THE LUNG.

Hollinshead AC, Stewart TH
(c/o Stewart), Ottawa General Hosp., 501 Smyth Road, Ottawa, Ontario K1H 8L6, Canada
Yale J Biol Med; 54(5):367-379 1981

Attempts to improve survival following curative surgery for non-small-cell lung cancer are reviewed. Most of these approaches have been designed to stimulate the resistance of lung cancer patients in a non-specific fashion. Living bacteria or products of dead bacteria have been given as adjunctive treatment. Various routes have been used; oral, intradermal, subdermal, or intrapleural, with either BCG or Corynebacterium parvum. No reproducible benefit has been observed. Levamisole has not been proven to be useful. Trials have yet to be completed to confirm the use of thymosin fraction V for small cell carcinoma in improving the effectiveness of chemotherapy. A pilot trial using specific active immunotherapy is described. Prolongation of survival 4 yr after closure of the trial in those patients immunized, compared with non-immunized patients, has prompted two further clinical trials. A small trial has confirmed the effectiveness of specific immunotherapy as adjunctive therapy for squamous cell carcinoma. A large multicenter trial in Canada and the United States should be completed and open to analysis in 1984 and may shed light on the role of tumor-associated antigens in stimulating specific resistance to lung cancer. (Author abstract) (66 Refs)

62. RECENT ADVANCES IN THE STUDY OF INTERFERON.

Ho M

Dept. Microbiology, Graduate Sch. Public Health, Univ. Pittsburgh, Pittsburgh, PA

Pharmacol Rev; 34(1):119-129 1982

Advances in understanding what interferon (INF) is, the mechanism of INF induction, how INF acts, the scope of INF biological activity, and potential clinical applications are reviewed, with emphasis on the biological and clinical aspects of INF use. Clinical trials with INF up to 1979 have included tests against osteogenic sarcoma, multiple myeloma, juvenile laryngeal papilloma, cervical carcinoma, breast cancer, non-Hodgkin's lymphoma, melanoma, and condyloma acuminata. The result of each trial has been alleged to be favorable. (81 Refs)

63. CYCLOSPORIN A: A NEW IMMUNE SUPPRESSIVE AGENT.

Sheil AG

Dept. Surgery, Univ. Sydney, New South Wales 2006, Australia

Med J Aust; 1(1):37-39 1982

The structure, administration, efficacy, and side effects of cyclosporin A (CSA), a new immunosuppressive agent, are described. CSA may be taken po since it is not inactivated by gut pH and enzymes. Im injection of CSA results in inflammation and absorption is uncertain. CSA has prolonged survival of kidney allografts in rats, rabbits, and dogs, of heart allografts in rats, pigs, and monkeys, and of bone marrow in rats and mice. In rats and rabbits, treatment for 2-3 wk give prolonged tolerance to organ grafts. In other species, continued CSA therapy is required. The mechanism of action of CSA is not fully understood. In vitro studies suggest that CSA exerts its effect on T cells by acting on T helper cells. Few side effects have been observed in laboratory animals treated with CSA. Clinical studies of CSA have been encouraging. Side effects of CSA include nephrotoxicity, hepatotoxicity, increased hair growth, gum hypertrophy, and mild tremors. No bone marrow toxicity has been observed. Among the first 134 patients treated with CSA, 4 cases of lymphoma have developed. The relationship between CSA treatment, immunosuppressive treatment in general, and Epstein-Barr virus and lymphoma is discussed. (29 Refs)

64. MOLECULAR CHARACTERIZATION OF INTERLEUKIN 2.

Gillis S, Mochizuki DY, Conlon PJ, Hefeneider SH, Ramthun CA, Gillis AE, Frank MB, Henney CS, Watson JD

Program in Basic Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104

Immunol Rev; 63:167-209 1982

Studies on the biology and biochemistry of interleukin 2 (IL-2) production and responsiveness are reviewed. Particular attention is given to preparative sodium dodecyl sulfate-polyacrylamide gel electrophoresis protocols, identification of human and murine tumor cell line sources of IL-2, and isolation and use of an anti-IL-2 monoclonal antibody. Recent progress in gene cloning to produce IL-2 in a bacterial or eukaryotic host is reported. (45 Refs)

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65. THE BIOCHEMISTRY, BIOLOGY, AND ROLE OF INTERLEUKIN 2 IN THE INDUCTION OF CYTOTOXIC T CELL AND ANTIBODY-FORMING B CELL RESPONSES.

Farrar JJ, Benjamin WR, Hilfiker ML, Howard M, Farrar WL, Fuller-Farrar J

Lab. Microbiology and Immunology, Natl. Inst. Dental Res., NIH, Building 30, Room 326, Bethesda, MD, 20205

Immunol Rev; 63:129-166 1982

The use of phorbol esters to optimize the production of immunoenhancing lymphokines by spleen cells, peripheral blood WBC, and T cell lines is reported. Recent findings on the molecular structure of murine thymoma-derived interleukin 2 (IL2) and the interaction of the factor with its receptor are described. The separation and characterization of a group of other lymphokines which are biochemically and functionally distinct from IL2, but which exhibit similar biological effects in some non-discriminating bioassays, is reviewed. Evidence for the lymphokine cascade is presented. (87 Refs)

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CLINICAL TRIALS

1. RECOMBINANT LEUKOCYTE A INTERFERON: PHARMACOKINETICS, SINGLE-DOSE TOLERANCE, AND BIOLOGIC EFFECTS IN CANCER PATIENTS.

Gutterman JU, Fine S, Quesada J, Horning SJ, Levine JF, Alexanian R, Bernhardt L, Kramer M, Spiegel H, Colburn W, Trown P, Merigan T, Dzlewanowski Z

Dept. Clinical Immunology and Biological Therapy, Univ. Texas M.D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030

Ann Intern Med; 96(5):549-556 1982

Sixteen patients with advanced cancer were treated with recombinant-DNA-produced pure leukocyte A interferon (IFLrA) intramuscularly in doses ranging from 3 to 198 x 10(6) units, with interval periods of 72 to 96 hr between doses. At the two lowest doses of 3 and 9 million units, there was a cross-over evaluation between IFLrA and partially pure leukocyte interferon (IFN-C) produced from human cells. The max observed serum concentration of IFLrA measured by enzyme immunoassay and bioassay increased with increasing doses. The mean serum concentrations of IFLrA and IFN-C were similar. Clinical effects produced by IFLrA and IFN-C were

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similar, including fever, chills, myalgias, headache, fatigue, and reversible leukopenia and granulocytopenia. Eight patients had transient and mild numbness of the hands or feet, or both. Three patients developed low titers of antibody to IFLrA. Seven of 16 patients showed objective evidence of tumor regression during the study. (Author abstract) (29 Refs)

2. CLINICAL AND IMMUNOLOGICAL STUDIES OF HUMAN FIBROBLAST INTERFERON.

Ezaki K, Ogawa M, Okabe K, Abe K, Inoue K, Horikoshi N, Inagaki J
Div. Clinical Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Res., Kami-Ikebukuro, Toshima-ku, Tokyo, Japan
Cancer Chemother Pharmacol; 8(1):47-55 1982

Clinical experience with human fibroblast interferon (HFIF) in various malignant diseases and immunological evaluations in patients receiving treatment with HFIF are described. Five patients with non-Hodgkin's lymphoma, five with multiple myeloma, four with stomach cancer, two with acute myelocytic leukemia, two with breast cancer, two with hepatoma, two with chronic lymphatic leukemia (CLL), two with ovarian cancer, one with malignant melanoma, and one with common duct cancer were entered into the study. Of the 24 evaluable patients, 2 achieved partial remission (PR: 1 with CLL, 1 with multiple myeloma) and 7 were considered to have stable disease (SD). The duration of response in the two PR patients was rather short, 8 and 9 wk. The disease progressed during HFIF treatment in these patients. Three of seven SD patients were in SD with daily or intermittent HFIF treatment, and these patients were progression free for 52 wk, 15 wk, and 9 wk. Of 10 patients who received 6 x 10(6) IU HFIF either from the start of treatment or from the middle of the course of treatment, 1 patient attained PR, 2 had SD, and the others had progressive disease (PD). Among five previously untreated patients two achieved PR, but the rest had PD. Results suggested that no correlation between the response to HFIF and previous chemotherapy exists. Clinical history for two PR patients (a 73-yr-old female with CLL and 49-yr-old female with multiple myeloma) and one SD patient (a 57-yr-old male with multiple myeloma) are summarized and presented. (13 Refs)

3. AMERICAN CANCER SOCIETY PHASE I TRIAL OF HUMAN INTERFERON BETA (IFN-BETA) (MEETING ABSTRACT)

Hawkins MJ, Krown SE, Borden EC, Real F, Krim M, Cunningham-Rundles S, Oettgen H, Fox RW, Stock CC, Rauscher FJ
University of Wisconsin, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:973 1982

Although human leukocyte interferon (alpha) has been utilized in most clinical trials to date, IFN-beta may have different biological and clinical effects. Sixteen patients with metastatic cancer were treated to determine the toxicities, pharmacokinetics and immunologic effects of IFN-beta. Enhanced NK cell cytotoxicity (NKCC) and fever were seen in some patients following an initial im injection despite the absence of detectable IFN titers. To determine the maximal tolerated dose (MTD) IFN-beta was administered as 10 daily iv bolus injections over 10 minutes and subsequently as 10 daily iv infusions over 6 hours. Toxicity was similar with bolus and infusion. Temperatures greater than 38.5 C were observed on 59/68 treatment days at 1 x 10(7) IU daily. At this dose rigors, fever, headache, malaise and lethargy were dose limiting. These side effects were partially controlled with antipyretics. In contrast to IFN-beta, these side effects decreased only slightly with continued administration. Hematologic depression occurred but was not dose limiting. Interferon titers were ten fold greater with bolus administration of 1 x 10(7) IU than with infusion and were still detectable 3 hours and 1 hour after bolus and infusion respectively. In general, NKCC was enhanced more by the bolus series of injections but increased more predictably 24-48 hours after administration of a single infusion injection. IFN-beta can be safely given in a repetitive iv dose schedule. A combination of bolus and infusion should produce high initial peak and sustained serum interferon levels and is a recommended dose schedule for Phase II clinical trials. (no Refs)

4. PHASE I TRIAL OF IMMUNOMODULATORY ACTIVITIES OF HUMAN LEUKOCYTE INTERFERON IN ADVANCED CANCER PATIENTS (MEETING ABSTRACT)

Neefe JR, Sreevalsan T, Bash JA
Lombardi Cancer Center, Georgetown University, Washington, DC, 20007
Proc Am Assoc Cancer Res; 23:969 1982

Twenty-five patients (pts) with advanced malignancy were treated in a phase I trial of human leukocyte interferon (IFN). Pts in groups of 3-5 received one dose of IFN, 0.5-60x10(6) units/m2. Immunomodulatory effects on natural killing (NK), antibody-dependent cellular cytotoxicity (ADCC), and monocyte-mediated cytotoxicity (MMC) were evaluated. Three pretreatment observations and posttreatment observations on d1, 3 and 7 were made. Peripheral blood mononuclear cells were separated into adherent (A) and non-adherent (NA) fractions by incubation on plastic coated with microexudate of the TU5 cell line. NA cells were tested for NK and ADCC in a standard 4 hr assay with K562 or EL4 coated with rabbit anti-mouse brain as targets. A cells were tested for MMC against 3H-thymidine labelled TU5 in a 48 hr assay. Assays were normalized with a frozen control. Most pts had ample levels of NK, ADCC, and MMC pretreatment. NK and ADCC activities changed in parallel, and a decrease was sometimes seen at d1. Two pts had significant increases in NK and ADCC at d3, with a fall to baseline at d7. One of these, with breast cancer, should stable disease. One pt had a striking decrease in NK and ADCC; his rhabdomyosarcoma continued in its previous pattern of rapid progression. A few pts had increased MMC at d3. There was a general correlation of IFN dose with peak serum IFN level and with duration of elevated IFN level, but no clear correlation of IFN level with changes in NK, ADCC or MMC. A single dose of IFN up to 60x10(6)/m2 does not produce consistent augmentation of NK, ADCC, or MMC. (no Refs)

5. RESPONSE OF A BLAST CRISIS OF CGL TO INTERFERON-ALPHA (MEETING ABSTRACT)

Hill NO, Khan A, Pardue A, Aleman C, Hilario R, Hill JM
Wadley Institutes of Molecular Medicine, Dallas, TX, 75235
Proc Am Soc Clin Oncol; 1:C-499 1982

Two patients with blast crisis of chronic granulocytic leukemia treated only with high dose intravenous human leukocyte interferon showed objective responses to this therapy, as did one additional patient with Philadelphia chromosome positive chronic granulocytic leukemia without blast crisis. The first patient initially received 500,000 units of interferon/kg daily in four divided doses. This resulted in a 95% decrease in blasts in 23 days of treatment. The second patient in blast crisis had a decrease in total white cells from a peak of 78,000 to 7,800 after three weeks of therapy at 1 million units/kg per day IV. Blasts decreased from a total of 10,800 to 73 absolute blasts/ul in that time. The patient without blast crisis had a decrease in the total white count from 94,000 to 21,000 as well as a reduction in spleen size. (no Refs)

6. RESPONSE OF DIFFUSE TRANSITIONAL CELL CARCINOMA TO LOW DOSE INTERFERON (MEETING ABSTRACT)

Aleman C, Khan A, Hill JM, Pardue A, Hilario R, Hill NO
Wadley Institutes of Molecular Medicine, Dallas, TX, 75235
Proc Am Soc Clin Oncol; 1:C-436 1982

Each of two patients receiving an intermittent low dose schedule of human leukocyte interferon for diffuse bladder carcinoma of transitional type experienced complete responses. These were verified by cystoscopic examination and biopsy prior to treatment and on a number of occasions thereafter. The schedule consisted of 3 million units of interferon intramuscularly per day for three weeks followed by four weeks of rest. The complete responses are verified by cystoscopy and biopsy at 11 and 7 months respectively. The second patient has refused further cystoscopies and biopsies, but has been asymptomatic for sixteen months. Six additional patients have so far been enrolled to a larger study including more advanced stages because of the striking findings in the first two patients. The clinical course of these patients will be summarized. (no Refs)

7. A PHASE I STUDY OF RECOMBINANT DNA PRODUCED LEUKOCYTE INTERFERON BY AN INTERMITTENT SCHEDULE (MEETING ABSTRACT)

Quesada JR, Gutterman JU, Fein S
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Soc Clin Oncol; 1:C-140 1982

A clinical study was conducted to determine the human tolerance and pharmacokinetics of intermittent doses of recombinant DNA produced pure leukocyte interferon (IFLrA) in cancer patients (pts). Twenty-five adults pts with advanced cancer (9 colon, 7 breast, 1 renal, 1 ovarian carcinomas; 6 lymphomas and 1 malignant fibrohistiocytoma) received IFLrA intramuscularly twice per week in groups of sequential escalating doses from 9 to 68 million units (MU). Fifteen pts are evaluable for pharmacological analysis and toxicity. Median maximum serum concentrations measured by bioassay were 107, 120 and 250 u/ml 8 hrs after a dose of 9, 18 and 36 MU respectively. Median serum concentration at 24 hrs for each of these doses were 10, 20 and 150 u/ml indicating slower clearance at higher doses. Pts received IFLrA from 3 to 12 weeks. The clinical side effects consisted of fever, chills and myalgias following almost all doses. These symptoms resolved spontaneously within 24 hrs. Headaches and gastrointestinal symptoms occurred frequently. Fatigue and anorexia persisted in all pts while on treatment. Dose reduction was indicated in one pt at 18 MU. Hematological toxicity consisted of reversible leukopenia and neutropenia. Median nadir was 2.4, 2.6 and 2.7x10(3) leukocytes mm-3 and 1.3, 1.7 and 1.3x10(3) neutrophils mm-3 at 9, 18 and 36 MU respectively. Hemoglobin decreased in 85% of the pts. No major adverse effects were seen in blood chemistries. Objective antitumor effect has been seen in 3 pts with lymphoma and 1 pt with breast cancer so far. (no Refs)

8. A MULTIPLE DOSE PHASE I TRIAL OF RECOMBINANT LEUKOCYTE A INTERFERON USING A 3 X WEEKLY SCHEDULE (MEETING ABSTRACT)

Sherwin S, Knost JA, Fein S, Abrams PG, Foon KA, Ochs J, Schoenberger C, Oldham RK
Biological Response Modifiers Program, National Cancer Institute-Frederick Cancer Research Facility, Frederick, MD, 21701
Proc Am Soc Clin Oncol; 1:C-139 1982

More than 50 patients with a variety of malignancies were treated in the first multiple dose Phase I trial of Recombinant Leukocyte A Interferon (IFL-rA). IFL-rA, which was provided by Hoffmann-La Roche Inc, has a specific activity of approx 2 X 10(8) units/mg. Patients received IFL-rA by intramuscular injection 3 X weekly for 28 days. Groups of 5 or more patients have been treated at the following dose levels: 1, 3, 9, 18, 36, 50, 68, 86, 100, 118 X 10(6) units. The toxicities observed resemble those of non-recombinant interferon and include fever, chills, fatigue, anorexia, myalgias, headache, and less frequently, nausea, vomiting and diarrhea. Dose-dependent leukopenia was common, generally reaching a plateau value after 1-2 weeks of treatment and returning quickly to baseline after treatgment was stopped. Thrombocytopenia was unusual. Significant hepatic transaminase elevations were not seen at doses less than 86 X 10(6) units. Patients were extensively monitored for serum interferon activity and with a panel of immunologic assays. Preliminary analysis of bioassay data reveals average peak serum interferon levels of 5, 20, 50, 10, 210, 235, and 250 units/ml, approx 6 hours after initial injections of 1, 3, 9, 18, 36, 50, and 68 X 10(6) units, respectively. Of the 42 patients who have completed treatment thus far, 11 patients with both hematologic and non-hematologic malignancies have demonstrated objective tumor regression thus demonstrating that IFL-rA has antitumor activity in vivo. (no Refs)

9. A PHASE I TRIAL OF LYMPHOBLASTOID INTERFERON USING A 6 HOUR INTRAVENOUS INFUSION (MEETING ABSTRACT)

Knost J, Sherwin S, Foon K, Abrams P, Ochs J, Williams R, Maluish A, Oldham R
Biological Response Modifiers Program, National Cancer Institute-Frederick Cancer Research Facility, Frederick, MD, 21701
Proc Am Soc Clin Oncol; 1:C-138 1982

Human Lymphoblastoid Interferon (HLI) has been administered by intravenous infusion to more than 10 patients with a variety of malignancies in an ongoing escalating dose Phase I trial. HLI is prepared from superinduced Namalva cells, and has a specific activity of 5x10(7) units/mg. Patients received a total of 5 cycles of treatment over a 5 week period. Each cycle consisted of 5 consecutive daily 6 hour infusions followed by a 2 day rest period. HLI dose was escalated at the beginning of each 5 day cycle in the following manner: 0.1, 1, 10, 30 and 50x10(6) units daily x 5 days. Patients were monitored at each dose level for serum interferon activity and with a panel of immunologic parameters. Commonly observed toxicities included fever, chills, anorexia, fatigue, headache, mild to moderate leukopenia, nausea and vomiting. These toxicities were dose-related generaly appearing at the 10x10(6) unit dose level. To date 2 patients have discontinued treatment due to HLI-related toxicity, both at the 30 x 10(6) unit dose level (1 patient due to incapaciting anorexia and fatigue and 1 patient due to SGOT evaluation). Preliminary analysis of the pharmacokinetic data indicates high levels of serum HLI activity have been obtained with peak levels of serum HLI activity have been obtained with peak levels of approximately 1000 units/ml and 7500 units/ml 6 hours after the start of the 10x10(6) unit and

50x10(6) unit infusions, respectively. After the 50x10(6) unit infusion serum HLI activity could be detected for up to 48 hours. (no Refs)

10. A PHASE I TRIAL OF TWICE DAILY RECOMBINANT HUMAN LEUKOCYTE A INTERFERON (IFL-RA) IN CANCER PATIENTS (MEETING ABSTRACT)

Leavitt RD, Duffey PL, Wiernik PH, Fein S, Sherwin S, Scogna D, Oldham R

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Proc Am Soc Clin Oncol; 1:C-162 1982

A phase I study of IFL-rA was performed in patients (pt) with advanced cancers and hematologic malignancies. At least 5 pt were entered at each dose level of 1,3,9,18,36,54 and 72 x 10(6) U/d and received IFL-rA intramuscularly twice daily for 28 days (d). Pharmacokinetics were determined. Results of immunologic monitoring will be reported separately. Constitutional symptoms are frequent. A 'flu-like' syndrome occurs early with chills, fever, headache, myalgias, and lethargy. Rapid tolerance to fever develops, but low grade fever may persist. Mild to moderate anorexia, nausea, vomiting, and diarrhea may occur. Fatigue, frequently progressive, is potentially dose limiting at 72 x 10(6) U/d. Transient paresthesias or numbness occurred in 2 pt. Dose related neutropenia and hepatotoxicity, unacceptably severe at 72 x 10(6) U/d, were tolerable at 54 x 10(6) U/d. Partial recovery from neutropenia often occurs while on treatment. Recovery from toxicity begins in days of stopping IFL-rA and was complete in all pt. Objective responses were seen in 7 pt (2 myeloma, plasmacytoma, nodular lymphoma, renal cell, adenocarcinoma of prostate and colon) receiving 36 or 54 x 10(6) U/d. Two of 3 measurable lesions completely regressed in the pt with renal cell carcinoma, who continued 54 x 10(6) U, 3x/wk. Phase II solid tumor studies are planned with 54 x 10(6) U/d given bid x28d. (no Refs)

11. A PHASE I TRIAL OF HUMAN LYMPHOBLASTOID INTERFERON (HULYINF) ADMINISTERED INTERMITTENTLY (MEETING ABSTRACT)

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Proc Am Soc Clin Oncol; 1:C-155 1982

In a study designed to describe dose dependent toxicity and biologic effects of HuLyINF, that material was administered to patients with advanced malignancy every 12 hours (q12h) intramuscularly for 14 doses to be repeated as a function of tumor response at 4 week intervals. Seven patients were entered at the initial dose level of 0.75 x 10(6) units q12h. Subsequent groups of 3 patients each have been entered at dose levels of 1.5, 3.0, 5.0, 8.0, and 12.0 x 10(6) units q12h. Patient accrual and dose escalation are ongoing. In the dosage range which has been studied, neither toxicity nor therapeutic efficacy showed a clear dose relationship. Toxicity noted includes fever +/- chills, moderate leukopenia, moderate thrombocytopenia, nausea/vomiting, headache, diarrhea, elevated SGOT/SGPT, rash, and decreased blood pressure. No life threatening toxicity has occurred. Partial responses have been seen in a patient with renal cell carcinoma at the 0.75 x 10(6) unit dosage and in a patient with diffuse histiocytic (large cleaved follicular center cell) lymphoma at the 1.5 x 10(6) unit dosage. Responses in patients with other tumor types, including 6 cases of breast cancer and 2 cases of CLL (chronic lymphocytic leukemia), have not been seen to date. Despite the frequent occurrence of leukopenia , HuLyINF was not directly toxic to cultured hematopoietic stem cells (CFU-GM). Pharmacokinetic data as a function of dosage will be presented. HyLyINF has shown tolerable toxicity and some, but limited, efficacy as administered. (no Refs)

12. PHASE I TRIAL OF HUMAN LEUKOCYTE INTERFERON (MEETING ABSTRACT)

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Proc Am Soc Clin Oncol; 1:C-154 1982

Human leukocyte interferon (IFN), was administered to 24 patients (pts), 21 with solid tumors and 3 with multiple myeloma, in a phase I trial. The study was conducted to establish a dose suitable for weekly intramuscular administration. Fourteen females and ten males had a median performance status of 1 on the ECOG scale (Range 0-3) and a median age of 47 (Range 19-72). All pts had received prior chemotherapy and eighteen were previously treated with radiation therapy. The schedule used was a single intramuscular dose of 0.5-60 x 10 units/m2. Some pts received additional IFN at weekly or monthly intervals. Fever was the most common toxicity occurring in virtually all patients at all dose levels. The fever usually appeared 2-4 hr following administration, lasted 12-24 hr, was above 39.5 C in 4 pts, and was associated with chills in 50% of pts. Mild nausea was seen in 7 pts and vomiting in four. Headaches were seen in 2 pts, weakness in 3, myalgias in 2, and transient disorientation in one. Hematological toxicity was minimal. Two pts developed leukopenia (WBC 3.0 x 10(3)/ul) 1-2 days following administration with a return to normal after five days. One severely anemic pt developed hypotension. No thrombocytopenia, renal, hepatic or neurological toxicity was noted. Toxicities appeared to be independent of dose of IFN up to 60 x 10(6)/m2. A minor response was noted in 1 pt with melanoma and in another with breast cancer; stable disease was seen in 1 pt with breast cancer and 2 others with myeloma. The maximum tolerated dose has not been reached and the study is ongoing. (no Refs)

13. INTERFERON TREATMENT FOR MULTIPLE MYELOMA.

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Clin Haematol; 11(1):211-220 1982

Clinical utility of interferon and of a potential interferon stimulator in 21 patients with multiple myeloma is discussed. Clinical trials with interferon in previously untreated patients showed a response in 3/12 cases (50% tumor mass reduction), some effect in 2/12 cases, and no effect in 7/12 cases. Remission duration ranged from 4-33 mo. Infusion of a derivative of a complex of polyriboinosinic and polyribocytidylic acids led to marked elevations of serum interferon in 18/20 patients with myeloma or lymphoma; no objective benefit was observed. (18 Refs)

14. PHASE I EVALUATION OF MVE-II IN MAN (MEETING ABSTRACT)

Rinehart JJ, Wilson HE, Neidhart JA
Division of Hematology/Oncology, Ohio State University, Columbus, OH, 43210
Proc Am Soc Clin Oncol; 1:C-145 1982

Pyran copolymer (1:2, copolymer of maleic anhydride and divinyl ether) has been shown in mice to induce interferon, activate macrophages, and have marked antineoplastic activity. A low mol wt fraction (15,500) of pyran copolymer (MVE-II) was relatively non-toxic in animals and was therefore chosen for clinical trials. Sixteen untreated patients (pts) with metastatic solid tumors were studied; 9 men, 7 women with a median age of 58 and near normal performance status. MVE-II was administered intravenously over 1 hour every two weeks. Pts received 250 (4 pts), 400 (4 pts), 600 (5 pts), and 900 (3 pts) mg/m(2)/dose. Pts were monitored at least twice weekly for standard parameters of toxicity and the following measures of immune function: Monocyte (Mo) antibody dependent cellular cytotoxicity (ADCC) and lymphocyte (LY) ADCC against CEM cells; LY natural killer activity against Molt-4; Mo to macrophage differentiation; LY transformation; and serum lysozyme and interferon levels. Clinical toxicity was minimal. Transient prolongation of the partial thromboplastin time was noted in 4 pts. Reversible proteinuria greater than 0.5 was noted after 2 courses in 1/7 pts evaluated receiving 400-600 mg/m(2)/dose. Both pts receiving 900 mg/m2 showed proteinuria after 2600 and 2700 mg/m2 total dose. No pt developed increased serum creatinine. Consistent immunologic effects were detected by measurement of LY ADCC. LY ADCC values obtained during six weeks of therapy were above mean baseline levels in 35/37, 26/49, and 21/24 individual determinations in pts receiving 400, 600 and 900 mg/m2 respectively. Elevated values tended to occur after the 2nd dose and return to baseline 2 weeks after the last dose. These data suggest that MVE-II has minimal toxicity in man and increases LY ADCC. (no Refs)

15. A PROSPECTIVE RANDOMIZED STUDY OF HORMONE-CHEMOTHERAPY WITH OR WITHOUT PSEUDOMONAS VACCINE (PV) IN METASTATIC BREAST CANCER (MBC) (MEETING ABSTRACT)

Hortobagyi G, Blumenschein G, Frye D, Yap Y, Schell F, Barnes B
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Soc Clin Oncol; 1:C-313 1982

One hundred fifty-four evaluable patients (pts) with MBC were treated with 5-fluorouracil, adriamycin and cyclophosphamide (FAC). Pts with estrogen receptor (ER)-positive or unknown tumors were also given tamoxifen (T) 6-8 weeks before starting FAC. All were randomized to treatment with (75) or without (79) PV. The median age was 57 yrs (range 30-75); median disease free interval: 24 months (0-180). ER status number of metastatic sites, menopausal status and dominant sites of disease were equally distributed in the PV+ and PV- groups. Thirty-four percent of 105 pts achieved a complete (CR) or partial remission (PR) after 6-8 weeks of T. Overall CR + PR, after T+FAC+/-PV was 84% (CR equals 29%): 65 of 75 (87%) with FAC +/- T and 65 of 79 (82%) with FAC +/- T+/-PV. Thirteen of 25 (52%) pts responsive to T achieved a CR after T+FAC+/-PV. In 11 pts who achieved only a PR after FAC, local therapy improved response to CR. After a median follow-up of 15 months less than 1/3 of pts have relapsed. Time to progression is projected to be significantly longer for pts responsive to both T and FAC (median greater than 23 months) than for pts responding only to FAC (16 months) or only to T (14 months). CR+PR and remission durations will be similar in FAC+PV and FAC groups. Gastrointestinal and hematologic toxicity were similar to our previous experience with FAC. PV induced fever, chills and local soreness in all pts. This combined modality therapy provides excellent palliation to pts with MBC. Improved CR and CR+PR rates have been achieved without significant added toxicity. (no Refs)

16. CMF +/- LEVAMISOLE (L) BREAST ADJUVANT CHEMOTHERAPY: 5 YEAR ANALYSIS (MEETING ABSTRACT)

Hakes TB, Currie VE, Kaufman RJ, Kinne D, Oettgen H, Pinsky C

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Proc Am Soc Clin Oncol; 1:C-319 1982

The MSKCC Breast Adjuvant Program entered 256 Stage II/III (+lymph nodes (LN) patients pts) post mastectomy between 3/76 and 3/80. Median follow-up is 48 mo with 28% followed over 60 mo. Pts were stratified for menopausal status and number of + axillary LN's and then randomized to 24 mo of Cyclophosphamide, Methotrexate, Fluorouracil (CMF) (Bonadonna) or CMF+L. Percentage CMF dose given, number of leukopenic episodes, amenorrhea, and quadrant of primary lesion were not correlated with DFS (disease free survival). ERP had no effect on DFS but was highly correlated with survival. Percentage ideal CMF dose given at 6, 12, 18 and 24 mo was 72, 65, 60, and 48% respectively and not correlated with DFS. Sites of recurrent disease include: 21% local , 21% regional, 41% systemic, and 17% local-systemic. Levamisole has not extended DFS or survival. (no Refs)

17. EFFICACY OF ORAL BCG THERAPY IN BREAST CANCER (MEETING ABSTRACT)

Serrou B, Cupissol D, Pujol H, Gary-Bobo J, Nguyen M, Gary-Bobo F, Favier F, Favier C

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Proc Am Soc Clin Oncol; 1:C-339 1982

One hundred and forty breast cancer patients (T1 T3, N0-N1b) were treated by irradiation then randomized into two groups which received either no adjuvant therapy or 150 mg Immun BCG-F (Pasteur Institute) per os once a week for one year. Patients were subdivided and randomized by stage. Sixty patients were assigned to each of three subgroups: T2-N1, T1-N1, T3-N1. The study has since ended and all patients have been followed for at least 17 months. No side-effects were observed for the BCG group (vomiting, diarrhea, etc) which necessitated cessation of treatment. At 3 years, disease free survival time is significantly (p less than 0.05) increased for patients on immunotherapy. The results based on patient stratification show a significant amelioration for patients treated by BCG for those initially classed as T1-N1 or T2-N1. No significant difference was observed for the T3-N1 patients. It was previously noted that patients who relapse after immunotherapy ultimately respond better to chemotherapy. The group receiving BCG also demonstrated signs of immunorestoration: ameliorated hypersensitivity skin tests (p less than 0.05); increased numbers of autorosette forming cells (p less than 0.05), but no significant increase in natural killer activity. (no Refs)

18. EFFECT OF PERORALLY ADMINISTERED BCG ON RECURRENT BREAST CANCER.

Kimura M
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J Surg Oncol; 20(1):65-69 1982

Twenty-eight patients with recurrent breast carcinoma were examined. Of them, 19 were evaluable for an oral route of BCG administration. Seven (37%) have had partial response (6 bone; 1 supraclavicular lymphonodus), 8 (42%) have shown no change, and 4 (21%) have shown failure. No remarkable side effects were observed by this administration. With regard to immunoresponse by oral administration of BCG, all tendencies such as increase of skin reactions, T-cells percent, PHA response of lymphocytes, and decrease of IgG FcR+ T-cells useful for estimating a good prognosis. These data suggest that peroral route of BCG may produce some beneficial effects for bone metastatic lesions of recurrent breast cancer. (Author abstract) (19 Refs)

19. ADJUVANT CHEMOTHERAPY FOR OPERABLE BREAST CANCER IN PREMENOPAUSAL WOMEN.

Falkson HC, Falkson G, Portugal MA, Schoeman HS, Louw EM
Dept. Cancer Chemotherapy, H. F. Verwoerd Hosp., Univ. Pretoria, Pretoria, South Africa
S Afr Med J; 61(18):651-655 1982

Surgery alone does not cure breast cancer, and adjuvant chemotherapy has changed the management of this disease. Data obtained in 81 premenopausal women with operable breast cancer, treated at our clinic, are presented. Patients with axillary node disease were treated on three different protocols: cyclophosphamide + methotrexate + fluorouracil + vincristine + prednisone (CMFVP), cyclophosphamide + methotrexate + fluoro-uracil (CMF), and CMF + immunotherapy with methanol extract residue of BCG (CMF + MER). Patient discriminants and treatment regimens are discussed. Analysis of the results obtained in 49 patients in one study showed an extension of disease-free survival to 4.25 yr, that CMFVP was superior to CMF with or without MER, and that immunotherapy was not beneficial. The literature is briefly reviewed and the motivation for our newer studies stated. (Author abstract) (15 Refs)

20. INTRAPERITONEAL IMMUNOTHERAPY OF HUMAN OVARIAN CARCINOMA WITH CORYNEBACTERIUM PARVUM (MEETING ABSTRACT)

Bast RC, Berek JS, Obrist R, Griffiths CT, Berkowitz R, Hacker NF, Parker L, LagasseLD, Knapp RC
Sidney Farber Cancer Institute, Boston, MA, 02115
Proc Am Soc Clin Oncol; 1:C-150 1982

Direct contact between immunostimulants and tumor cells has favored effective immunotherapy in animal models and clinical trials. In previous studies of a murine ovarian carcinoma, IP administration of C parvum inhibited IP tumor growth and augmented the activity of peritoneal cells for antibody dependent cell mediated cytotoxicity (ADCC). Doses and schedules of C parvum that augmented ADCC also potentiated serotherapy with specific rabbit heteroantiserum. C parvum (0.25-4.0 mg/m(2)) has been administered IP on 1-8 occasions to 11 patients with peritoneal implants of ovarian carcinoma that had failed to respond completely to cytoreductive surgery and combination chemotherapy. An additional 2 patients have been treated in an adjuvant setting following a complete response to chemotherapy. Fifty-one courses of IP immunotherapy have been assocated with fever greater than 101 F (25%), abdominal pain (88%), nausea (57%), vomiting (29%) and hypotension (6%). Of 11 patients with residual disease, 8 have been treated for a sufficient period to evaluate response. Among these 8 patients, 2 have had complete responses (5 and 12 mo), 1 a partial response, 2 stabilizaiton of disease and 3 disease progression. Administration of C parvum IP has augmented the ability of human peritoneal cells to lyse human ovarian carcinoma cell lines in the presence of specific rabbit heteroantiserum. C parvum administered IP appears to inhibit the growth of human ovarian carcinoma and may prove useful for modulating the activity of human effectors of ADCC. (no Refs)

21. IMMUNOTHERAPY OF ELDERLY PATIENTS WITH COLORECTAL CARCINOMA.

Navarra S, Melita P, Di Mauro S
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Minerva Med; 73(18):1225-1232 1982

The effectiveness of adjuvant immunotherapy was studied in 83 patients (beyond the age of 60 yr) with colorectal carcinoma. Dukes' Stage C was diagnosed in 62 patients who were subjected to radical surgery. Thirteen of these patients (Group A1) were subjected to postoperative chemotherapy with the combination of 5-fluorouracil (5-FU: 400 mg/square meter (m2)) and carmustine (BCNU: 40 mg/m2); 22 others (Group A2) to the same chemotherapy with BCG treatment (0.2 mg), and 27 to chemotherapy and levamisole treatment (150 mg/day). Dukes' Stage D was diagnosed in 2 patients who were subjected to palliative surgery. Five of these 21 patients were then subjected to chemotherapy with 5-FU + BCNU (Group B1), 7 to chemotherapy with BCG treatment (Group B2) and 9 to chemotherapy with levamisole treatment (Group B3). The 3-yr survival rates were 53.6% in A3. The 1-yr survival rates were 60% in Group B1, 55.5% in B2 and 57.1% in B3. All patients in Groups B1 and B2 died within 2 yr, and all patients in B3 within 3 yr. Adjuvant immunotherapy was found to increase the survival rates and to improve the quality of life in Dukes Stages C patients and to improve the quality of life in Dukes Stage D patients. (27 Refs) (In ITA)

22. COMBINED ADJUVANT THERAPY OF RADICALLY OPERATED COLORECTAL CANCER PATIENTS. (CHEMOTHERAPY, RADIOTHERAPY, AND MER-BCG).

Robinson E, Bartal A, Cohen Y, Haim N, Mohilever J, Mekori T
Dept. Oncology, Nothern Israel Oncology Center, Rambam Medical Center, Haifa 35245, Israel
Cancer Chemother Pharmacol; 8(1):35-40 1982

Long-term follow-up of 73 patients who had undergone curative surgery for colorectal cancer and adjuvant therapy is reported. Patients were randomized into groups to be treated with radiochemotherapy (RC) or RC plus methanol extraction residue of BCG (RCM). Forty-four patients had Dukes' C colorectal cancer (DCC) and 29 Dukes' B2 rectosigmoid cancer (DRC). The major characteristics of these patients are summarized. The RCM and RC subgroups were similar, except that in Stage B2 the female/male ratio was higher in the RC-treated than in the RCM-treated patients. The actuarial survival (AS) at 54 mo was 78% in the RCM subgroup and 26% in the RC subgroup. The difference was statistically significant. At 54 mo the difference in AS was no longer significant (53% for the RCM-treated and 25% for the RC-treated patients). In DRC patients, the AS at 42 mo was significantly better in the RCM-treated patients than in those treated with RC. In DCC of the proximal colon a better survival at 54 mo was obtained in nine patients treated with 5-fluorouracil (5-FU) and methanol extraction residue of BCG than in eight patients treated with 5-FU alone. The survival and disease-free interval at 48 mo in DRC patients were 55% and 46%, respectively, for the RCM-treated patients and 61% and 31% in RC-treated patients. In patients with DCC, the disease recurred in 8 (36.4%) of the RCM group and in 12 (54.5%) of the RC group. In patients with DRC, recurrence developed in six (46.2%) RCM-treated patients and in six (37.5%) RC-treated patients. (32 Refs)

23. LEVAMISOLE AND 5-FLUOROURACIL IN METASTATIC COLORECTAL CARCINOMA (MEETING ABSTRACT)

Davis TE, Borden EC, Wolberg WH, Crowley JJ
University of Wisconsin Clinical Cancer Center, Madison, WI, 53792
Proc Am Soc Clin Oncol; 1:C-396 1982

In animal tumor models, the most consistent effects of levamisole (lev), a synthetic phenylimidazothiazole, have been observed when used in combination with chemotherapy. We therefore initiated a trial in which patients with metastatic colorectal carcinoma, who were of good performance status (PS) and had not received prior radiotherapy or chemotherapy were prospectively randomized to cyclic loading courses every 6 weeks of 5-fluorouracil (5-FU) (12 mg/kg intravenously daily x 5; then 6 mg/kg on alternate days to toxicity) or 5 FU and lev (2.5 mg/kg orally on days 28, 29, 35 and 36 of each cycle). A total of 82 fully eligible and evaluable patients were entered on this trial. The only patient or disease characteristics to significantly influence survival were PS and presence of measureable disease. Patients who received 5 FU and lev survived longer than those who received 5 FU alone. Adjustments according to a Cox regression model for the influence of PS or measureable disease did not influence this treatment difference. There also were no significant differences in the severity of toxicities between the two treatments (Fisher's exact test). (no Refs)

24. CHEMOIMMUNOTHERAPY IN DISSEMINATED MELANOMA: A SOUTHWEST ONCOLOGY GROUP STUDY (MEETING ABSTRACT)

Costanzi JJ, Al-Sarraf M, Frank J
University of Texas Medical Branch, Galveston, TX, 77550
Proc Am Soc Clin Oncol; 1:C-655 1982

This study was a prospective randomized study in patients with disseminated malignant melanoma who were tested with either carmustine (BCNU), Hydroxurea, and dacarbazine (DTIC) (BHD) or BHD plus Levamisole (CT+IT) or high dose DTIC plus Actinomycin D (DIC-DAC). A number of patient factors were examined and the randomization did achieve a balance between treatment arms. Two hundred and twenty-one patients were treated and responses were noted in 14/49 on BHD (29%), 24/84 (29%) for CT+IT, and 21/88 (24%) for DIC-DAC. Previous extensive experience with BHD noted a response rate of 30%. When all patients were considered there was no statistical difference in survival but of those who responded the BHD responders had a median survival of 28 weeks, CT+IT-20 weeks and DIC-DAC 47 weeks. Certain factors were statistically significant in determining longer survival. These included female sex, better performance status, absence of brain, liver, or bone involvement, hemoglobin greater than 11.0, and lymphocyte counts greater than 2000 per dl. Toxicity was acceptable with the majority of the patients experiencing mild to moderate nausea, vomiting, and leukopenia. One patient had life threatening leukopenia which was reversible. (no Refs)

25. ACTINOMYCIN-D PLUS 5-(3,3-DIMETHYL-1-TRIAZENO)-IMIDAZOLE-4-CARBOXAMINE (DTIC) WITH OR WITHOUT INTRAVENOUS CORYNEBACTERIUM PARVUM IN METASTATIC MALIGNANT MELANOMA.

Robidoux A, Gutterman JU, Bodey GP, Hersh EM
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Cancer; 49(11):2246-2251 1982

Chemotherapy and chemoimmunotherapy of Stage IV B malignant melanoma were compared in 88 patients. Chemotherapy consisted of 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC) 250 mg/M2 of the body surface area daily x 5 days and actinomycin-D 2 mg/M2 on day 1 repeated every 3-4 wk. Chemoimmunotherapy consisted of the same regimen plus corynebacterium parvum 2 mg/M2 iv daily for 14 days before every third cycle of chemotherapy, plus 2 mg/M2 iv daily on days 7 and 14 of each 21-28 day chemotherapy cycle. There was 32 evaluable chemotherapy and 33 evaluable chemoimmunotherapy patients and the groups were well balanced for clinical and pathologic as well as prognostic variables. The complete and partial remission rates, remission and survival durations, and hematologic and gastrointestinal toxicities were different in the two randomized groups being 6 and 3%, 9 and 9%, 7.6 and 12 mo, 8.8 and 6.0 mo, 20 and 16%, and 62 and 70%, respectively for these parameters. This difference was not statistically significant. Therefore, it can be concluded that the results of chemotherapy with actinomycin-D plus DTIC were not substantially different from those reported using DTIC alone, and that we cannot recommend the addition of actinomycin-D to DTIC for palliative management in these patients. Furthermore, C parvum immunotherapy did not add to chemotherapy in terms of remission rate, remission duration, or survival for patients with Stage IV B malignant melanoma. (Author abstract) (17 Refs)

26. REDUCED INCIDENCE OF LOCO-REGIONAL RECURRENCES IN MELANOMA USING BCG IMMUNOTHERAPY AFTER SURGERY (MEETING ABSTRACT)

Paterson AH, Willans D, Jerry LM, McPherson TA
Cross Cancer Institute, Edmonton, Alberta, Canada
Proc Am Soc Clin Oncol; 1:C-662 1982

A prospectively controlled, randomized clinical trial was carried out to determine whether a combination of local perilesional intradermal (ID) and systemic oral BCG immunotherapy given after surgery to patients with Stage 1 melanoma would reduce the overall recurrence rate and improve survival. Patients with Stage 1 melanoma, Clarke's level (CL) 3-5 were eligible for trial entry, and after surgical wide excision and consent, were randomly allocated to either routine follow-up or adjuvant BCG immunotherapy. Immunotherapy consisted of ID BCG 40 mgs by Heaf Gun around the site of local surgery followed by oral BCG 40 mgs for 5 days each month for one year. ID BCG was then repeated at the same time and oral BCG was continued for one further year. One hundred and seventy-one patients have been entered into the trial, 83 in the treatment group and 88 in the control group. Side-effects and toxicity have been minimal. There have so far been 40 recurrences: 15 in the treatment group and 25 in the control group. Twenty-six patients have died: 10 in the treatment group and 16 in the control group. Using this form of immunotherapy, there has been a modest reduction in the incidence of local and regional recurrence as site of first recurrence but not of distant metastases. The overall recurrence rates show a trend in favor of the BCG group, which is not statistically significant. (no Refs)

27. CHARACTERIZATIONS OF THE HUMORAL RESPONSE OF RENAL CELL CARCINOMA PATIENTS RECEIVING SPECIFIC ACTIVE IMMUNOTHERAPY (MEETING ABSTRACT)

Miller GA, Pontes JE, Huben R, Wajsman Z, Goldrosen MH
No affiliation given
77th Annual Meeting of the American Urological Association, Inc May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

A Mixed Hemadsorption Assay (MHA), a measure of IgG sensitization to cell surface antigens, was used to monitor the humoral response of renal cell carcinoma patients receiving specific active immunotherapy with irradiated autologous tumor cells and Corynebacterium parvum as adjuvant. Autologous tumor cells were used as targets for MHA. Tumor cells were isolated from frozen tumor chunks by sequential enzymatic digestion with collagenase, hyaluronidase, pronase and DNAse followed by density gradient centrifugation through hypague-ficoll. To date, 9 of 12 non-fibroblastic primary autologous cultures have been established. These cultures consist of three cell types. The most common was classified as 'clear cell type'. Eighteen serum specimens from 6 renal cell carcinoma patients undergoing specific immunotherapy were evaluated by the MHA assay against autologous tumor cells. Ten of 18 serum specimens demonstrated significant binding to autologous tumor cells. The endpoint titers ranged from 1/16 to 1/512. Eight of these 10 positive responses were observed during specific active immunotherapy. Temporal studies of patient MM revealed the loss of MHA activity one month after surgery. After immunotherapy had begun a MHA response was observed. This MHA response correlated with cessation of progression of disease. (no Refs)

28. CLINICAL EVALUATION OF INTERFERON AGAINST ADVANCED UROLOGICAL CANCER (MEETING ABSTRACT)

Marumo K, Hagiwara M, Deguchi N, Jitsukawa S, Murai M, Nakazono M, Hata M, Tazaki H
No affiliction given
77th Annual Meeting of the American Urological Association, Inc., may 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Six patients with hypernephroma with subsequent development of distant metastasis after having nephrectomy and one patient with adenocarcinoma of the urinary bladder accompanied by cutaneous and hepatic metastasis were treated with human lymphoblastoid interferon (HLBI) of 300 million units/day given intramuscularly. Two patients with advanced cancer of the prostate were treated with human fibroblast interferon (HFI), the dose ranging from 150 to 300 million units/day intravenously. In patients with hypernephroma, partial response as evidenced by more than 50% reduction in pulmonary lesion at 3 months was noted in one patient, stable disease for a period from 31 to 85 days by unremarkable changes on chest x-ray in 3 patients and progressive disease in 2 patients. Resolution of cutaneous lesion accompanied by disappearance of hyperbilirubinemia and reduction of serum CEA (carcinoembryonic antigen) level was noted in the patient with adenocarcinoma of the bladder. In patients with cancer of the prostate, improvement of bony lesion was noted by bone scanning in one patient and stable disease in the other. No serious adverse effect was noted. In order to determine the therapeutic dose of interferon, growth inhibition assay was undertaken, utilizing an established cell line from hypernephroma (KU-2) as target. Growth of KU-2 cells of 1x10(4)/ml. On the other hand, serum concentration of interferon reached its highest point of 200IU/ml at 6 hours after administration of 300 million units. Therefore at least 300 million units of interferon would be required to obtain any clinical benefit. (no Refs)

29. CHEMOIMMUNE PROPHYLAXIS OF SUPERFICAL BLADDER CANCER (MEETING ABSTRACT)

Adolphs HD, Bastian HP
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

We developed the concept of chemoimmune prophylaxis of bladder cancer on the basis of experimental findings. In January 1978, we introduced this concept of recurrence prophylaxis of superficial bladder cancer as a pilot study into clinical praxis. Fourteen days after complete tumor resection, 700 mg/m2 cyclophosphamide was given intravenously. Two weeks thereafter, we began intravesical BCG instillations using 120 mg strain Connaught BCG/50 normal saline. At the same time BCG skin scarification was performed. This intravesical and percutaneous BCG treatment was repeated 5 times in weekly intervals. We have currently treated more than 80 patients with T1 grade I, II or III transitional cell carcinomas. Our preliminary results reveal a decrease of tumor recurrences in the BCG treated patient group compared with a retrospective group of 65 well controlled untreated cases. Reviewing our results theoretically 3 possible immunological mechanisms have to be considered: 1) Cyclophosphamide inhibits the precursors of suppressor T cells resulting in stimulation of the cytotoxic immune response against the tumor. 2) The humoral immune response is depressed by cyclophosphamide with consequent inhibition of immune complex formation correlating with tumor enhancement. 3) BCG exerts a tumor destructive effect by means of a chronic granulomatous inflammation and a nonspecific stimulation of tumor immunity. (no Refs)

30. RESULTS OF A STUDY ON THE TREATMENT OF NON-HODGKIN'S LYMPHOMA USING A COMBINED MODALITY APPROACH (MEETING ABSTRACT)

Pleumann L, Havemann K, Diehl V, Gassel WD, Schumacher K, Langer B, Hassenstein E, Heb K
Abteilung Hamatologie/Onkologie und Abteilung fur Strahlentherapie, Medizinischen Hochschule Hannover, Karl-Wiechert-Allee 9, D 3000 Hannover 61, W. Germany
J Cancer Res Clin Oncol; 103(Suppl):A15 1982

The results presented were obtained from a current multicenter randomized treatment study on high-grade, previously untreated non-Hodgkin's lymphoma (NHL), stages II to IV, in 43 patients. All patients (ages 25 to 75 years) received from 6 to 9 courses of chemotherapy using a modified CHOP regime (CVC (cyclophosphamide) 750 mg/m2 IV over 21 days; ADM (adriamycin) 50 mg/m2 IV over 21 days; VCR (vincristine) 1.4 mg/m2 IV over 21 days; Prednisolone 100 mg oral days 1-4, 25 mg oral day 5). After the fourth course of chemotherapy, they received 'involved field' radiotherapy of all primary manifestations using 25 GyHD. One group of patients was additionally intervenously treated with 3 mg/m2 Corynebacterium parvum (Coparvax) on day 6 of each chemotherapy course. After seven and ten therapeutic courses, respectively, patients were restaged. Patients with complete remission (CR) received maintenance therapy consisting of COP in increasing intervals over a period of two years. At the time of evaluation, Group 'A' (with C parvum) consisted of 21 patients, and Group 'B' (no C parvum) of 23 patients. There was no statistically significant difference between A and B. Since the addition of C parvum to the regimen did not have any demonstrable effect, groups A and B were pooled for the analysis. An overall response rate was 72% with 64% in CR. Sixty-nine percent of centroblastic NHL, 85% of immunoblastic NHL and 53% of lymphoblastic NHL went into CR. The latter group often showed a progression, not seldom transforming into therapy-resistant ALL. During the time of follow-up, only one patient in CR suffered a relapse. We conclude that the chosen scheme of therapy is highly effective in centro- and immunoblastic NHL. There was only moderate treatment related toxicity and most patients were treated on an out-patient basis. (no Refs)

31. ROLE OF IMMUNOTHERAPY IN COMPLEX TREATMENT OF LUNG CANCER.

Trapeznikov NN, Gorodilova VV, Babakova SV, Kadagidze ZG, Trakhtenberg AKh, Mar'in ND, Drakina LV, Boguslavskii VM
No affiliation given
Vopr Onkol; 28(2):51-56 1982

The results of clinical trials of the efficacy of immunotherapy in lung cancer (LC) patients are reported. Evaluation of the immune status of 117 LC patients showed significant inhibition of the functional activity of immunocompetent cells. The degree of inhibition of cellular immunity was directly related to the Stage of LC. Efficacy of intrapleural administration of BCG vaccine was studied in 48 patients with Stage I-III LC. The patients were randomized into two groups. Group 1 (23) received preoperative immunotherapy with BCG vaccine and isoniazide (100 mg, tid, for 12 wk). Group 2 (25) underwent surgery alone (control). Side-effects of immunotherapy included transient fever, fatigue, and loss of appetite. The 2-yr survival rates after BCG immunotherapy were 100% for Stage I, 90.1% for Stage II, and 56.6% for Stage III, compared with 85.4%, 72.8%, and 40.1%, respectively, after surgery alone. (8 Refs) (In RUS)

32. COMBINATION CHEMOTHERAPY, RADIOTHERAPY, AND BCG IMMUNOTHERAPY IN LIMITED SMALL-CELL CARCINOMA OF THE LUNG. A SOUTHWEST ONCOLOGY GROUP STUDY.

McCracken JD, Chen T, White J, Samson M, Stephens R, Coltman CA, Saiki J, Lane M, Bonnet J, McGavran M
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Cancer; 49(11):2252-2258 1982

From November 1976 to March 1979 the Southwest Oncology Group treated 298 patients with limited (disease confined to the chest and encompassed by one radiotherapy port) small-cell carcinoma of the lung with combination chemotherapy and radiotherapy with or without BCG immunotherapy. Two induction chemotherapy programs were utilized: (1) cyclophosphamide, vincristine, methotrexate, fluorouracil; or (2) cyclophosphamide, doxorubicin, and vincristine. Patients received 4,500 rad of radiation therapy to the bulk primary tumor and 3,000 rad to whole brain followed by maintenance chemotherapy. One-half of all the patients were randomized to receive one vial (5 x 10(8)) of high viability Pasteur BCG by scarification technique given on days 8 and 15 of each 21-28 day treatment cycle. Increased granulocytopenia accompanied the addition of BCG immunotherapy. Patients receiving BCG achieved a response rate of 49% vs those patients not receiving BCG of 44% (p = 0.579). Median response duration was 40 wk for the BCG arms and 38 wk for the arms without BCG; survival was no different, 42 wk for the BCG arms vs. 50 wk for the arms without BCG. In patients who responded to therapy and survived longer than 1 yr, those who continued to receive BCG therapy demonstrated a slight, yet significant, survival benefit over those patients not receiving BCG (93 wk vs 81 wk, p = 0.03). It appears that BCG immunotherapy has no beneficial effect on response rate, duration of response, or survival in programs using chemotherapy and radiotherapy for control of limited small-cell carcinoma of the lung except in this small group of long-term survivors. (Author abstract) (17 Refs)

33. DOXORUBICIN, CYCLOPHOSPHAMIDE AND VP16-213 (ACE) IN THE TREATMENT OF SMALL CELL LUNG CANCER.

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Cancer Chemother Pharmacol; 7(2/3):187-193 1982

Use of doxorubicin (A) 45 mg/m2 iv day 1, cyclophosphamide (C) 110 mg/m2 day 1, and VP16-213 (E) 50 mg/m(2)/day iv days 1-5 for treatment of small cell lung cancer is reported. One hundred and seventy-four patients were randomized for three sequential studies: ACE versus ACE + methanol extracted residue of BCG (MER) immunotherapy (38 patients), or ACE versus ACE alternating with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), methotrexate less than vincristine and procarbazine (109), or ACE versus ACE II (ACE with continuous E 100 mg/m(2)/day x 5 days; 27). Regardless of the additional therapies, the ACE combination produced greater than 90% response; in limited disease a complete response (CR) frequency of 65% was achieved. In extensive disease, CR freuency was 40%. Response frequency and survival were identical in the first two studies with 20-30% of patients with limited disease as long term survivors; one late relapse occurred (greater than 3 yr). Patients who achieved CR had a significantly longer survival regardless of other factors such as performance status or extent of disease. Cranial irradiation was useful in prevention of CNS metastases in patients who achieved CR. These results demonstrate that ACE chemotherapy combined with prophylactic cranial irradiation for cerebral metastases is highly effective for treatment of small cell lung cancer regardless of extent of disease. (34 Refs)

34. BCG IMMUNOTHERAPY OF LUNG CANCER IN A DISTRICT ONCOLOGY DISPENSARY. I. STUDY OF 860 PATIENTS WITH HISTOLOGIC DIAGNOSIS.

Hadziev S, Mandulova P, Kavaklieva-Dimitrova J, Fenev K, Spassova M, Madzarova S
District Oncology Dispensary, Plovdiv, Bulgaria
Neoplasma; 29(1):93-110 1982

The investigation refers to lung cancer patients registered in an oncology dispensary from 1965 to 1975. The conventional treatment (surgery, radiotherapy and chemotherapy) has covered 35.9% of all patients, whereas immunotherapy with BCG or with its soluble fraction has been applied in 46.2% of them. Immunotherapy has mainly been applied to epidermoid carcinoma and large-cell carcinoma. Comparing the survival of immunotherapy treated with non-immunotherapy treated patients it was found that in Stage I-II group the difference in favor of immunotherapy was significant in the 2nd yr of observation and in Stage III group a significant difference was found in all observation periods (1-5 yr). In Stage I-II the 5-yr survival rate of immunotherapy treated patients (13.2%) was similar to the survival rate of operated patients (13.7%). Immunotherapy in large cell carcinoma showed significantly better results than immunotherapy in epidermoid carcinoma. Immunotherapy with BCG and F70 was applied as an independent treatment of lung cancer. When applied to patients primarily operated, radiation or chemotherapy treated, the survival was significantly higher than the survival of patients submitted to conventional treatment or to immunotherapy separately. (Author abstract) (27 Refs)

35. EFFECT OF THE METHANOL EXTRACTION RESIDUE OF BACILLUS CALMETTE-GUERIN IN ADVANCED HODGKIN'S DISEASE.

Cooper MR, Pajak TF, Nissen NI, Brunner K, Stutzman L, Bank A, Falkson G, Barker BE, Haurani FI, Richards F, Gottlieb A, Holland JF
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Cancer; 49(11):2226-2230 1982

One-hundred-ninety-six patients with Stage III and IV Hodgkin's disease were prospectively randomized to receive either treatment with the methanol extraction residue of Bacillus Calmette-Guerin (MER/BCG) or no immunotherapy. Prior to the MER/BCG randomization, patients received six courses of induction and 2 yr of maintenance chemotherapy so that a group with a presumptively low tumor burden could be established. Only patients achieving a complete remission were evaluated. During the first 2 yr of immunotherapy, the MER/BCG group had a relapse frequency twice that of controls. The overall crude relapse frequency and disease-free survival were similar between the two treatment groups. The MER/BCG dose schedule used in this study was associated with a high frequency of unacceptable toxicity. Ulcerations of greater than 1 cm occurred in one-third of the patients with associated pain, fever, and occasional lymphadenopathy. A high degree of patient noncompliance (36%) was observed. Age ($p = 0.002$), prior radiotherapy ($p = 0.032$), and chemotherapy ($p = 0.044$) were prognostic factors found to significantly influence remission duration. These factors were balanced between patients treated with immunotherapy and those who were not. MER/BCG therapy did not significantly delay or prevent relapse. (Author abstract) (32 Refs)

36. TREATMENT OF ADVANCED HODGKIN'S DISEASE: 10-YEAR EXPERIENCE IN THE EASTERN COOPERATIVE ONCOLOGY GROUP.

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Cancer Treat Rep; 66(4):855-870 1982

Between 1972 and 1981, the Eastern Cooperative Oncology Group completed two major studies of advanced Hodgkin's disease. The first trial, EST 2472, demonstrated that the five-drug combination of carmustine (BCNU), cyclophosphamide, vinblastine, procarbazine, and prednisone (BCVPP) is an effective alternative to mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) chemotherapy. Although the complete remission (CR) rate for BCVPP (77%) was similar to that for MOPP (73%) in this randomized trial, the choice of induction chemotherapy significantly influenced CR duration. Patients achieving CR with BCVPP had a significantly greater disease-free survival than those who achieved CR with MOPP (65% vs 50%, respectively, at 5 yr, $p = 0.02$). Overall survival is not different at this time between patients who received BCVPP and those who received MOPP. BCVPP produced significantly less gastrointestinal toxicity and neurotoxicity than MOPP. There was no influence on CR duration or survival with maintenance chemotherapy or BCG immunotherapy when compared to no further treatment. In the second trial, EST 1476, there was only a 58% CR rate with six cycles of low-dose bleomycin-MOPP induction chemotherapy. Complete responders and continuing partial responders were then randomized to receive either non-cross-resistant chemotherapy with doxorubicin, bleomycin, vinblastine, and DTIC (dacarbazine) (ABVD) or low-dose radiotherapy to all sites of pretreatment involvement except bone marrow. Fifty percent of the partial responses were converted to CR with either ABVD or radiotherapy consolidation. The overall Cr rate at the end of consolidation was 68%. At the present time, there is no significant difference in disease-free or overall survival between ABVD and radiotherapy. (Author abstract) (19 Refs)

37. MURINE MONOCLONAL ANTIBODY THERAPY IN TWO PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA.

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Blood; 59(5):1036-1045 1982

We infused the murine monoclonal antibody T101 into two patients with advanced refractory chronic lymphocytic leukemia (CLL) after confirming its reactivity with their CLL cells. One patient received doses of 1, 3, and 12 mg; the second patient received 10 mg. Antibody was delivered over 10-15 min. The major observations were: (1) T101 murine monoclonal antibody did bind to cells with T65 surface antigen and saturated these cells in vivo; (2) cells that bound T101 disappeared from the circulation by 2 hr after treatment, as evidenced by a marked drop in lymphocyte counts; (3) T101 serotherapy resulted in some intravascular cell injury associated with sequestration and probably destruction in the liver and lung; (4) free serum T101 was demonstrable, but disappeared by 2-4 hr after infusion; (5) rapid infusion of T101 did not induce significant modulation of T65; (6) rapid infusion of greater than 10 mg of T101 was associated with significant systemic reactions. Monoclonal antibodies may someday have an application in leukemia therapy, but additional experimental trials are clearly indicated. (Author abstract) (26 Refs)

SYNTHETIC IMMUNOTHERAPEUTIC AGENTS

38. AUGMENTATION OF NATURAL KILLER CELL ACTIVITY IN NORMAL AND TUMOR BEARING BALB/C MICE BY LEVAMISOLE (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:1060 1982

Natural killer cell (NK) activity is an important factor in the immune constituent of young mice and seems to play a role in immune surveillance mechanisms against tumors. Levamisole (LMS) had exhibited immunoregulatory and anti-tumor properties but its effects on NK activity has not been investigated. Whether LMS exert any regulatory function on NK activity in 8 wk old male BALB/c mice was the question posed in this study. Two groups of mice were inoculated with 1x10(6) viable cells (in minimal essential medium) of the 50th transplant generation of a MTV induced mammary tumor which originated from a spontaneous tumor in multiparous BALB/cfC3H female. At the time of inoculation of tumor cells and at 24, 48, and 72 hr thereafter, one group was inoculated with LMS (50 mg/kg of body weight). A third group received LMS alone; controls received no treatment. Administration of LMS caused a significant increase in NK activity of normal non tumor bearing mice above controls. In mice inoculated with tumor cells alone, an increase in NK activity was observed above controls. This could be further augmented above controls by LMS administration in tumor bearing mice. LMS augmentation of NK activity was detected as early as 48 hr and up to 144 hr post inoculation. (no Refs)

39. EFFECTS OF LEVAMISOLE AND CONTINUOUS BLADDER INSTILLATION OF MITOMYCIN-C ON TRANSPLANTED URINARY BLADDER CANCER (MEETING ABSTRACT)

Koseki K, Akaza H, Hara T, Kobayashi K, Umeda T, Niijima T, Kitagawa H, Iwaguchi T
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

We made following experimental model systems to study effects of levamisole and continuous bladder instillation of mitomycin C (MMC), using osmotic mini-pump (ALZA, USA), on the transplanted urinary bladder tumor. BBN (4-(butylnitrosoamino)-1-butanol) induced tumor cells were implanted in the bladder wall of inbred ACI/N rats. By osmotic mini-pump, implanted subcutaneously, MMC at the various concentrations were instilled in the bladder. Levamisole, as a immunomodulator, was subcutaneously injected on day 7 after tumor cells implantation at the concentration of 5 mg/kg. Experimental rats were divided into the following 5 groups. 1) Tumor cells implantation only. 2) Tumor cells implantation and levamisole injection. 3) Tumor cells implantation and instillation of saline. 4) Tumor cells implantation and instillation of MMC. 5) Tumor cells implantation, instillation of MMC and levamisole injection. Experimental rats were killed on day 7 and 14 in groups 1), 3) and 4), and on day 14 in groups 2) and 5). Tumor growths were not completely inhibited when 0.34 mg/mini-pump of MMC were instilled to the bladder tumors made by the implantation of 5x10(4) tumor cells. Histologically, cellular degeneration and necrosis were observed on superficial layer of MMC treated groups, however tumor cells were alive in the profunder layer. On group 5), prominent lymphocytic infiltrations in the tumor tissues were observed. (no Refs)

40. AN AUTORADIOGRAPHIC ANALYSIS OF MURINE LUNG, LIVER AND SPLEEN CELLS FOLLOWING TREATMENT WITH A TRITIUM-LABELED IMMUNOPOTENTIATING AGENT (CP-46,665) (MEETING ABSTRACT)

Hightower JA, Gangemi JD
Departments of Anatomy and Microbiology and Immunology, School of Medicine, University of South Carolina, Columbia, SC
Anat Rec; 202(1):145 1982

Clearance and organ localization of the synthetic lipoidal amine CP-46,665 was examined in C3H mice following intravenous inoculation. Autoradiographs of lung cytocentrifuge preparations revealed a moderate accumulation of the drug in alveolar macrophages within 2 hours, heavier accumulation by 24 hours and persistance at lower levels for 7 days or longer. Concomitantly, label was observed in hepatocytes, Kupffer cells and a variety of cell types in the red pulp of the spleen inculding macrophages, neutrophils, lymphocytes and developing erythrocytes. Neither splenic white pulp nor draining lymph nodes were heavily labeled. In vitro suppression of tumor cell growth and synthesis of prostaglandin E2 (PGE2) by alveolar macrophages recovered from treated mice suggests that CP-46,665 activates these cells more quickly (2 days versus 5-9 days) and at lower dosages (0.3 mg/kg versus 6 mg/kg) than the classical bacterial agent, Corynebacterium parvum. These data suggest that the novel synthetic lipoidal amine CP-46,665 is localized in a number of organs and cell types and that one of the consequences is the rapid activation of murine alveolar macrophages. (no Refs)

INTERFERON

41. REGULATION OF NATURAL KILLER CELL (NKC) ACTIVITIES IN CANCER PATIENTS AND NONCANCEROUS INDIVIDUALS BY RECOMBINANT INTERFERON-ALPHA-CLONE-A (R-IFN-ALPHA-A) (MEETING ABSTRACT)

Lotzova E, Savary CA, Gutterman GU, Hersh EM, Quesada JR, Pestka S

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Proc Am Assoc Cancer Res; 23:1058 1982

Since r-IFN-alpha A has therapeutic potential in cancer, we have studied its effect on NKCs-the cells implicated as one of the components of tumor immunity. NKC activity of peripheral blood was measured against K-562 tumor cell line in a 3 hr 51Cr release assay. We observed significant augmentation of NKC cytotoxicity in 11 noncancerous individuals after treatment with r-IFN-alpha-A, independent of whether the effector cells were preincubated with r-IFN-alpha-A, or r-IFN-alpha-A was added directly to the cultures. NKC augmentation and its degree was dependent on the concentration of r-IFN-alpha-A employed; cytotoxicity was augmented with concentration of 10(3) units/ml, but was significantly less, or not potentiated with 10(2) or 10 units/ml. Kinetic studies indicated that the augmentation of NKC cytotoxicity was prompt, since the effect was observed as early as 10 min after incubation of effector cells with r-IFN-alpha-A. Despite the augmentation of lytic activity of NKCs, the NKC-tumor cell-binding properties were not changed by r-IFN-alpha-A. NKC cytotoxicity of 9 cancer patients, with various diagnosis, was also modulated by r-IFN-alpha-A. Four to 8 hr after a single im injection of 50-68 x 10(6) units of r-IFN-alpha-A, a decrease of NKC cytotoxicity was observed in all patients. The subsequent NKC modulation depended on the NKC phenotype of cancer patients, ie, 6 of 6 low NKC responders were potentiated 24 hr after a single r-IFN-alpha-A injection, whereas 3 of 3 high NKC responders were not significantly augmented. These data indicate that r-IFN-alpha-A is a potent NKC stimulatant. (no Refs)

42. DIETHYLDITHIOCARBAMATE (DDC)-MEDIATED BLOCKADE OF NATURAL KILLER (NK) CELL ACTIVITY: RELATIONSHIP TO INTERFERON (IFN) EFFECTS (MEETING ABSTRACT)

Edwards BS, Fox RW, Merritt JA, Borden EC
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Proc Am Assoc Cancer Res; 23:1062 1982

The ability of IFNs to augment NK cell activity and the ability of anti-IFN antisera to block, not only augmentation, but also the basal expression of NK cell activity, suggest that IFNs serve a fundamental role in NK cell regulation. DDC blocks IFN-mediated development of the antiviral state, possibly by its inhibitory effects upon superoxide dismutase. Therefore, to further examine the role of IFNs in NK cell function, we treated human peripheral mononuclear cells with DDC and assessed NK cell reactivity to K562 target cells in 6-hr Cr-51 release assays. At concentrations of 10(-6) to 10(-4), DDC inhibited basal NK cell activity 50-95% without affecting cell viability. In 2 of 3 experiments, DDC-inhibited NK cells spontaneously recovered function within 24-48 hr of treatment. One hr treatment with IFN, sufficient to enhance NK cell activity of controls 2-3 fold, failed to boost activity of DDC-treated NK cells. However, continuous incubation of DDC-pretreated cells with IFN for 24 hr resulted in levels of NK cytotoxicity equal to or greater (depending upon DDC pretreatment dose) than in control cells exposed only to IFN. We conclude that a DDC-sensitive enzyme(s) is required for IFN-mediated stimulation of NK cells. Reduction of basal NK cell activity by DDC is furthermore consistent with a role for IFN in NK cell functional maintenance. (no Refs)

43. PARAMETERS OF INTERFERON ACTION. NATURAL KILLER (NK) ACTIVATION DURING A PHASE II TRIAL (MEETING ABSTRACT)

Ernstoff MS, Hebert GZ, Kirkwood JM
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Proc Am Assoc Cancer Res; 23:975 1982

Eleven patients were treated with Finnish Red Cross (Cantell) human interferon alpha (Hu IfNalpha) supplied by the American Cancer Society. Patients were treated with im Hu IFNalpha at 1, 3, or 9 x 10(6) units daily for 42 days. Nine of these have undergone serial studies for serum interferon levels and fresh peripheral blood NK assays against the K562 leukemia line at effector to target ratios of 25, 50, and 100:1. Absolute values of lytic function were followed over time. At a 50:1 ratio baseline NK lysis was 50:1% +/-13.6 SEM in the group overall, and rose to peak values at day 8 in all patients with low initial NK function. Four patients who manifested high initial NK function (55-100% lysis) failed to augment values significantly at any time during the trial. Tabulation of the aggregate results show that at days 2, 8, 15, and 42 NK lysis rose from baseline to 66.8% +/-10.6, 81.2% +/-7.1, 63.1% +/-11.6 and 66.8% +/-11.4. Optimal in vivo activation of NK function is manifest after 2 days and before 15 days of Hu IFNalpha treatment as given here. Based on these and other reported NK data, rational new phase I trial designs ought include pulsed regimens of less than 14 days. We are piloting a program of pulsed daily im Hu IFNalpha therapy given for five days every three weeks using Hu IFNalpha obtained from a regional program in conjunction with the Connecticut Red Cross. Intermittent regimens may sustain optimal NK function along with other parameters during therapy with Hu IFNalpha. (no Refs)

44. MACROPHAGE ACTIVATION BY INTERFERON: DISSOCIATION BETWEEN TUMORICIDAL CAPACITY AND SUPPRESSIVE ACTIVITY.

Boraschi D, Soldateschi D, Tagliabue A
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Eur J Immunol; 12(4):320-326 1982

Resident peritoneal macrophages (M phi) from untreated mice and inflammatory M phi induced by a sterile irritant were able to exert significant suppressive activity on lymphocyte functions. M phi-mediated suppression was evident in lymphocyte proliferation and in a proliferation-independent lymphocyte response (ie lymphokine production). The lymphokine macrophage-activing factor (MAF), which enhances tumoricidal capacity of inflammatory but not of resident M phi in vitro, was ineffective in modulating suppressive activity of both resident and inflammatory M phi. In contrast, a significant effect on M phi-mediated suppression was observed upon treatment with IFN-beta. In fact, suppression of lymphoproliferation and of lymphokine production by either resident or inflammatory M phi was significantly decreased or abolished by IFN-beta. Like MAF, IFN-beta was able to increase M phi cytotoxicity against tumor cells. Such an effect, however, was evident in both resident and inflammatory M phi, thus confirming different M phi activation mechanisms for MAF and IFN-beta. These data indicate that IFN-beta acts mainly on mature M phi, which thus appear as the major M phi type involved in suppression. The contrasting effects of IFN-beta on M phi suppression and on M phi-mediated cytotoxicity strongly suggest a dissociation between the two induction mechanisms of suppression and cytotoxicity. The in vivo relevance of these two IFN activities was demonstrated by treating mice with the potent IFN inducer polyinosinic polycytidylic acid (poly(I) . poly(C)). M phi from poly(I) . poly(C)-primed mice simultaneously showed enhanced tumoricidal activity and complete abolishment of suppressive capacity. (Author abstract) (38 Refs)

45. IMMUNOPHARMACOLOGY OF HUMAN LYMPHOBLASTOID INTERFERON (IF) IN MAN (MEETING ABSTRACT)

Laszlo J, Huang A, Brenckman W, Koren H, Cianciolo G, Buckley CE, Cox E, Cashdollar W, Metzgar R, Lucas VS, Jeffs C, Dorenkamp S
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Proc Am Assoc Cancer Res; 23:966 1982

A study was designed to test the pharmacologic effects and immunologic changes produced by varying doses of intramuscular IF. The study design tested single and repeated (15 over five weeks) incremental doses of IF in 17 ambulatory patients with cancer who were suitable for these biologic and pharmacokinetic experiments. Single injections of 1-5 megaunits produced fever, chills, malaise, myalgia, and headache. Fever attenuated with repeated administration so that higher doses could be tolerated: the other constitutional symptoms were dose-limiting however. Reproducible laboratory effects produced by interferon were: acute drop (12 hrs) followed by persistent rises in both lymphocyte counts and natural killer cell activity. Natural killing activity was augmented by a factor of 1:1 to 5 over baseline levels, and could be predicted by in vitro IF stimulation. Erythropoiesis as measured by in vitro colony growth was suppressed by IF; 60% reduction in CFU-E (colony forming unit) and 75% reduction in BFU-E (blast forming unit) were noted at 49 days of IF treatment whereas myelopoiesis (GMCFC growth demonstrated slight reduction (20). Surprisingly, there was no activation of monocyte function by in vivo IF administration, as measured by polarization, chemotaxis, phagocytosis, or superoxide generation. No significant changes occurred in skin testing or immunoglobulin levels. The problem of selecting a suitable therapeutic dose remains, given the lack of clear-cut dose-response effects. (no Refs)

46. INCREASED SURVIVAL AND INTERFERON INDUCTION BY BCG CELL WALL IMMUNOTHERAPY IN PET DOGS WITH MALIGNANT MAMMARY TUMORS (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:964 1982

In a prospective BCG cell wall (BCG-CW) immunotherapy study designed to simulate human clinical trials, adult pet dogs with naturally occurring primary mammary tumors were randomized after biopsy confirmation of malignancy to receive an intratumoral injection of either BCG-CW (4 mg/ml) or placebo 4 weeks prior to definitive tumor surgery or to receive surgery only (SO). Serial serum specimens were collected over a 30 month clinical course from pets in the 3 groups: 24 BCG-CW injected dogs, 22 placebo injected dogs and 20 SO treated dogs. High titers of interferon (IF) were detected by plaque reduction assays in 20 of 24 (83.3%) BCG-CW treated dogs, but not in dogs in the 2 control groups. Radioimmunoassays detected significant increases in BCG-CW antibody levels in 23 of 24 BCG-CW treated dogs, but not in the other subjects. Surgical tumor excision did not change serum BCG-CW antibody levels, but it reduced both the numbers of IF positive dogs and the serum IF titers in dogs in the BCG-CW injected group and in the SO treated group. The mean time of tumor-free survival from completion of therapy was significantly extended, and significantly greater numbers of dogs survived tumor-free in the BCG-CW injected group compared with dogs in the other 2 control groups. These results suggested a strong, direct relationship between tumor-free survival and levels of circulating BCG-CW antibody and IF induced during BCG-CW therapy. (no Refs)

47. ANTITUMOR ACTIVITY OF INTERFERON: IN VITRO STUDIES ON HUMAN MELANOMA (MEETING ABSTRACT)

Fisher PB, Kellogg C, Sheffield K, Graham GM, Grant S, Pestka S, Oster MW, Weinstein IB
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Proc Am Assoc Cancer Res; 23:898 1982

In the present study we have used a human melanoma cell line (HO-1) to evaluate the ability of both crude KG-1 (crude-IF) and bacterial-cloned (IF1rA) human leukocyte interferon (IF) to inhibit the in vitro growth of tumor cells in agar suspension. We found that both types of IF caused a 50% inhibition in cloning efficiency of this cell line in agar (LD50) at concentrations in the range of 125-175 units/ml. The cloning efficiency was reduced greater than 80% by 1000 IF units/ml with HO-1 cells not previously exposed to IF, and also with HO-1 cells that were grown as monolayer cultures for one week in the presence of 1000 units/ml of IF1rA prior to plating in agar. A series of colonies that survived growth in agar in the absence or presence of 500-1000 units/ml of either crude IF or IF1rA were isolated from the agar plates and then maintained in monolayer culture in the absence of IF. When these clones were reseeded into agar 5 subcultures later, these clones displayed a 9-29 fold greater cloning efficiency than the parental cell line. When rechallenged for growth in agar in the presence of 1000 units IF1rA/ml, the clones that had not been previously exposed to IF exhibited a 74+/-12% inhibition in cloning efficiency, whereas the clones that had been previously exposed to IF displayed only a 51+/-7% reduction in cloning efficiency. The selection of variants of melanoma cells that have increased resistance to growth inhibition by IF may explain the limited success of this agent in the treatment of human melanoma. (no Refs)

48. INTERFERON INCREASES HLA SYNTHESIS IN MELANOMA CELLS: INTERFERON-RESISTANT AND -SENSITIVE CELL LINES.

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Proc Natl Acad Sci USA; 79(10,part1):3265-3269 1982

We report that human leukocyte interferon preparations increase the expression of beta2-microglobulin by 100-200% on the surface of normal fibroblast and melanoma cell lines sensitive to interferon. This increase in expression can be correlated with an increase in HLA synthesis as measured by incorporation of [35S]methionine in these antigens. This enhanced HLA synthesis, which is 5-to 17-fold, is time dependent and dose related. Synchronized cells in the G0/G1 phase of the cell cycle appear to be more sensitive to this interferon action. Neither an increase in surface expression nor in HLA synthesis is observed in a melanoma cell line resistant to the antiviral and antigrowth effects of interferon. Furthermore, there appears to be a stronger correlation between this increased HLA synthesis and the antiviral function that between it and the antiproliferative action of interferon. (Author abstract) (18 Refs)

49. EFFECT OF INTERFERON ON THE GROWTH OF A MURINE BLADDER TUMOR, MBT-2 (MEETING ABSTRACT)

Ratliff TL, Oakley DM, Shapiro A, Catalona WJ
No affiliation given
77th Annual Meeting of the American Urological Association, Inc May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

We examined the effect of murine L cell interferon (IFN beta) and immune interferon (IFN gamma) on the growth of a transplantable N-[4-(5-nitro-2-furyl)-2-thiazolyl]formide (FANFT)-induced bladder tumor, MBT-2. IFN beta was generated by stimulation of L929 cells with Newcastle Disease Virus and purified to a specific activity of approximately 10(6) units/mg protein. IFN gamma was prepared by stimulation of murine splenocytes with phytohemagglutinin and purified to a specific activity of approximately 10(4) units/mg protein. C3H/HeJ female mice were injected in the hind leg with 10(4) viable MBT-2 cells, and therapy was initiated on the same day by injection 500 units IFN gamma, 1000 units IFN beta into the tumor-bearing leg. Therapy was continued for 7 consecutive days and at 3 day intervals thereafter for 4 injections. Controls include injection of a mock IFN preparation and phosphate buffered saline (PBS). Mice treated identically were sacrificed at various times during treatment to monitor immune parameters. The results show a significant inhibition of tumor outgrowth by both IFN gamma and IFN beta as compared to controls. Eighteen days after tumor injection 80% of the mock- and 90% of the PBS-treated animals possessed palpable tumors while after 37 days only 20% of the IFN beta and 30% of the IFN gamma treated mice had tumors. Studies on the immune response show a significant increase in natural killer cell activity in both IFN gamma and IFN beta treated animals. (no Refs)

50. INTERFERON AS MODIFIER OF ESTROGEN RECEPTORS IN CANCER TISSUES (MEETING ABSTRACT)

Dimitrov NV, Myer C, Einhorn S, Strander H, Cantell K
Michigan State University, Lansing, MI, 48824
Proc Am Assoc Cancer Res; 23:946 1982

The purpose of these studies was to determine the effect of human interferon on the activity of estrogen binding protein in breast cancer tissue. Human breast cancer tissues, a variety of breast cancer cell lines and normal uterus as a control were used as a source of estrogen binding protein. Tissue and cell homogenates were incubated with various doses of highly purified human leukocyte interferon (IFN). The effect of the IFN was recorded as two-three fold increase in the cytosol estrogen receptors. The optimum response was obtained with doses ranging between 10 and 1000 U/mL of incubation medium. The escalation of the dose up to 5000 U/mL did not increase or inhibit the binding activity. Cytosol fractions with zero or low binding activity did not respond to IFN treatment. Addition of antibodies against IFN resulted in abrogation of the IFN effect. Incubation of homogenates with mock IFN did not show any increase in the estrogen binding activity. These experiments indicate that the increase of the estrogen receptor activity is due to IFN and not to possible contaminants. Preliminary results from experiments with a variety of IFN-alpha and IFN-beta preparations indicated no difference in the biological modification of the estrogen binding protein. The increase of estrogen receptors activity in breast cancer may have an important clinical application if the effect of IFN in vivo is identical to that obtained in our experiments. (no Refs)

51. SERUM AND CEREBROSPINAL FLUID (CSF) PHARMACOKINETICS OF RECOMBINANT LEUCOCYTE A INTERFERON (IFLRA) IN MONKEYS (MEETING ABSTRACT)

Riccardi R, Kramer MJ, Trown PW, O'Neill D, Levine AS, Poplack DG
National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:799 1982

We investigated the serum and CSF pharmacokinetics of IFLrA following IM, IV and IT administration in rhesus monkeys. Animals with subcutaneously implanted reservoirs were utilized for these studies. Following IV and IM injections of 2.5 and 5x10(6) U/kg, serum samples were taken at 2, 5, 10, 15, 30, 45, and 60 mins, and 1.5, 2, 3, 5, 8 and 12 hrs. After IV administration at the two different doses, serum levels of about 2.5x10(4) U/ml and 6x10(4) U/ml were achieved at 2 mins and declined rapidly, with an alpha and beta half life of about 16 and 340 mins respectively. Following administration of identical doses of IM IFLrA, serum levels peaked at 4 hrs. In contrast to IV injection, serum IFLrA levels were sustained for approximately 6 hrs following IM administration. However, the area under the curve (AUC), a measure of the amount of drug present in the systemic circulation over time, was similar in both circumstances. Peak CSF levels following both IV and IM administration were below 0.05% of the peak serum levels. Following intraventricular administration of 1x10(6) U of IFLrA, CSF levels declined with a single half life of about 2 hrs. No major toxicity was observed following the three different routes of administration. Our data indicate that 1) although different peak levels of IFLrA were observed following IV or IM administration, the AUC were similar in each case; 2) only a fraction of circulating IFLrA penetrates into the CSF following parenteral administration; and 3) sustained CSF IFLrA levels can be achieved following intraventricular administration. (no Refs)

52. CHANGES IN DNA-POLYMERASE AND THYMIDINE KINASE ACTIVITY DURING INTERFERON TREATMENT.

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Biochem Biophys Res Commun; 105(4):1569-1576 1982

The effect of human interferon beta (IFN-beta) on the human glioma cell line, U-251 MG, was investigated. Exponentially growing cells treated with IFN exhibited a dose-dependent growth depression observed after 3 days, and an increase in the amount of cells in S phase. However, the activity of DNA polymerase was decreased to 30% of control levels at day 5 with 1,000 Units/ml of IFN-beta. This depression in enzyme activity may be explained by an inhibitory effect of IFN on the increase of enzyme activities induced by events in late G1 or early S, or by the induction of diffusable factors depressing enzyme activities. Starved cells were induced to cycle and DNA content was followed cytofluorometrically. S phase started approx 12 hr after addition of serum to synchronized cells and cells entered G2 at 21 hr. In contrast, IFN-treated cultures initiated S but accumulated in that phase. At the start of S phase, both DNA polymerase and thymidine kinase activity increased, although the rate of increase was markedly reduced by treatment with IFN. No inhibitory factor could be identified in the IFN treated cultures. It is probable that IFN has a direct effect on the induction of the studied enzyme activities, thus affecting virus replication. (18 Refs)

53. ACTIVITY OF HUMAN LEUKOCYTE INTERFERON IN A HUMAN TUMOR CLONING SYSTEM.

Von Hoff DD, Gutterman J, Portnoy B, Coltman CA
Dept. Medicine, Div. Oncology, Univ. Texas Health Science Center at San Antonio, San Antonio, TX, 78284
Cancer Chemother Pharmacol; 8(1):99-103 1982

The human tumor cloning system of Hamburger and Salmon was used to investigate the antitumor effect of human leukocyte interferon (IF) in material from 29 bone marrow aspirations, 53 tumor biopsies, 14 paracenteses, and 10 thoracenteses in 106 patients with advanced malignancies. Colonies in culture were formed in 62/106 attempts. IF caused a greater than or equal to 70% decrease in tumor colony forming units (TCFU; at a concentration of 1,000 U/ml) in only five cultures, one each of lymphosarcoma cell leukemia, small cell lung cancer, adenocarcinoma of the lung, breast cancer, and pancreatic cancer. IF caused an increase in the number of colonies over control growth in three cultures: one adenocarcinoma of the lung (82% increase), and two ovarian cancers (39% and 141% increase). Of the 62 dose-response studies conducted, IF had minimal or no effect on 15 different tumors in vitro, even at concentrations as high as 1,000 U/ml; only three patients (lymphosarcoma cell leukemia, small cell lung cancer, and pancreatic carcinoma) had greater than or equal to 70% decrease in TCFUs at the highest concentration of IF used (1,000 U/ml). The antitumor effect of IF was studied in one patient with lymphosarcoma cell leukemia with an 85% decrease in the number of colonies formed in vitro. Clinically, IF resulted in a decrease in the size of the lymph nodes, but circulating leukemic blast cells continued to be present. The cloning system may be useful for identifying patients who might experience an antitumor effect from IF. (26 Refs)

54. EVALUATION OF EFFECTS OF RECOMBINANT LEUKOCYTE A INTERFERON ON THE NUTRITIONAL STATUS OF PATIENTS (MEETING ABSTRACT)

Scogna DM, Hetrick K, Riggs CW, Sherwin S, Fein S, Oldham RK
Frederick Memorial Hospital, Frederick, MD, 21701
Proc Am Soc Clin Oncol; 1:C-225 1982

Gastrointestinal toxicity including anorexia, nausea and vomiting and diarrhea as well as fatigue appear to be dose-dependent side effects of patients receiving recombinant Leukocyte A Interferon (IFL-rA). IFL-rA was administered intramuscularly in a multiple dose phase I protocol, either 2x/day or 3x/wk for 28 days with dose ranges from 1-118x10(6) units. IFL-rA is greater than 98% pure and has a specific activity of 2x10(8) units/mg protein. Sixty-three patients have been evaluated to date. The followng parameters were evaluated comparing baseline to day 28 data: weight, total protein, albumin, absolute lymphocyte count, and performance status. The factors, with the exception of absolute lymphocyte count, represent a significant decrease compared to baseline but did not lead to discontinuation of therapy in any cases. Further correlation with IFL-rA dose, disease and responses will be presented. Further nutritional assessements of patients receiving IFL-rA need to be made in a prospective manner. (no Refs)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

55. LONG TERM PROTECTION AGAINST BLADDER CANCER PRODUCED BY IMMUNOTHERAPY (MEETING ABSTRACT)

Lamm DL, Reichert DF
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Long term tumor free survivors from experiments using BCG immunotherapy were randomized and tested for long term protective immunity against murine bladder carcinoma (MBT-2). Fifty-one mice that had survived tumor challenge and fifteen previously unchallenged mice received an intradermal inoculation of 1 x 10(6) MBT-2 cells. Immunotherapy consisted of intraperitoneal Levamisole, intralesional live Tice strain BCG, or intralesional saline given at 24 hours. The 15 controls received saline. All three group of survivors had less tumor growth than control. The BCG group, but not the Levamisole group, had significant inhibition of tumor growth compared with the long term survivors receiving saline. A second experiment compared 22 non-immune mice, 21 mice pre-immunized intravenously with 300 ug of BCG cell walls (CW), and 18 mice surviving MBT-2 after live BCG treatment. Non-immune and survivor groups were randomly subdivided into saline or treatment groups. CW pre-immunized mice were divided into matching groups according to footpad response to PPD. All mice received tumor followed at 24 hours by intralesional administration of the test agent. The CW pre-immunized and non-immune mice received either the immunostimulant P3+Re-Glycolipid or the carrier solution. The group of survivors received either saline or live BCG. Both BCG and saline survivor groups showed significantly less tumor growth and longer survival than non survivor controls. Animals treated with P3 Re-Glycolipid with or without preimmunization with CW did not differ from control. Footpad response to PPD did not correlate with tumor growth. (no Refs)

56. CHEMOIMMUNOPROPHYLAXIS OF AN EXPERIMENTAL BLADDER CANCER WITH RETINOIDS AND BACILLUS CALMETTE-GUERIN (MEETING ABSTRACT)

Pang AD, Morales A

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Recently evidence has appeared indicating that the retinoids may enhance the host immune response and this has been advanced as an additional mechanism for their antitumor effect. We have investigated 2 different retinoids: 13-CIS-retinoic acid (Ro 4-3780) and all-trans-retinoic acid (Ro 10-9359) alone and in combination with BCG in the prophylaxis of an experimental bladder neoplasm. Groups of animals bearing a syngeneic bladder tumor were treated with either of the retinoids alone or in combination with non-specific immunotherapy. It was found that treatment of mice with Ro 4-3780 did not significantly reduce the incidence of tumor takes. Treatment with Ro 10-9359, on the other hand, induced significant protection against tumor take in 66.7% of the animals. The addition of BCG immunizations to either of the retinoid treatments showed that no therapeutic gain was obtained by the combination of Ro 4-3780 + BCG but that Ro 10-9359 + BCG further reduced the incidence of tumor takes by 30.8%. There were also marked differences in the incidence of tumor regression among groups. For the BCG group alone it was 45.5%. In animals receiving Ro 4-3780 alone it was only 10% but, the addition of BCG to this retinoid resulted in a significant increase incidence of tumor regression to 41.7%. Ro 10-9359 alone induced tumor regression in 12.5% of mice but Ro 10-9359 + BCG resulted in an 83% incidence of regression which is highly significant. (no Refs)

57. COMPLICATIONS OF INTRAPLEURAL BCG IN THE TREATMENT OF OPERABLE NON-SMALL-CELL BRONCHIAL CARCINOMA.

Law MR, Lam WK, Studdy PR, Pugsley WB, Hodson ME

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Br J Dis Chest; 76(2):151-156 1982

Seventy-eight patients entered a randomized study of postoperative intrapleural BCG in the treatment of bronchial carcinoma. Thirty-nine patients received BCG (Tice strain), of whom 17 took isoniazid, and there were 39 controls. There was a high rate of complications related to the use of intrapleural BCG, in both isoniazid and non-isoniazid treated groups. Postoperative infections occurred in eight BCG treated patients and one control; seven BCG treated patients but only one control developed prolonged postoperative chest pain. Empyema developed 6 mo postoperatively in three of the BCG treated group. Furthermore BCG conferred no survival advantage at 1 yr. We considered the complications to be of sufficient severity and incidence to discontinue the study. (Author abstract) (23 Refs)

58. IMMUNOPROPHYLAXIS OF A MURINE BLADDER CANCER WITH HIGH DOSE BCG IMMUNIZATIONS.

Pang AS, Morales A
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J Urol; 127(5):1006-1009 1982

The immunoprophylactic effect of Mycobacterium bovis, strain Bacillus Calmette-Guerin (BCG) was studied in a syngeneic bladder tumor system. Injection of a high dose of viable BCG 10 days before tumor cell challenge induced a 46% reduction in tumor take. On the other hand, no protection against tumor take was afforded by the simultaneous administration of BCG and tumor cells. Complete tumor regression, however, was observed in a number of animals of the two groups receiving BCG: 90% in the group receiving the vaccine and the tumor simultaneously and 50% in those being immunized 10 days before tumor challenge. These findings indicate that high dose, viable BCG immunization favorably alters the course of this experimental tumor. (Author abstract) (25 Refs)

59. HYPERCOAGULABILITY AFTER IMMUNOTHERAPY WITH CORYNEBACTERIUM PARVUM IN MAN.

Harenberg J, Baumgartner A, Fritze D, Zimmermann R
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Blut; 44(4):241-247 1982

Results of coagulation studies in a controlled randomized trial of 18 female patients with metastatic breast cancer receiving low iv doses of Corynebacterium parvum and chemotherapy are reported. Fibrinopeptide A (FPA) was measured as a sensitive parameter for detecting plasma hypercoagulability. C parvum was administered according to a random procedure on day 15 (Group I), or day 1 of the cytostatic cycle (Group II), or was not applied at all (Group III). There was no premedication with steroids or antipyretics. FPA increased in Group I from an av of 1.5 nanog (ng)/ml to 12 ng/ml 1 hr and to 18.6 ng/ml 2 hr after start of therapy. In Group II, FPA changed from 4.5 ng/ml (before) to 36 ng/ml (1 hr), 57.5 ng/ml (2 hr), 12.9 ng/ml (4 hr), and to 3.6 ng/ml (24 hr). In Group III, no significant changes in FPA were observed. The platelet count decreased continuously in all treatment groups, with no differences between groups. There were no significant changes in prothrombin time, fibrinogen concentration, activated partial thromboplastin time, and thrombin clotting time. Factor VII:C and Factor VIII:Ag were not affected. The ethanol gelation test was always negative. The euglobulinlysis showed a tendency to become shorter 1 and 2 hr after the beginning of therapy in Group I and II. The concentration of plasminogen and the antiplasmins aplha1-antitrypsin, alpha2-macroglubulin, and antithrombin III were not affected by any of the treatments. All patients of Group I and II developed an increase in rectal temperature with a max of 38.8 C after start of therapy. (21 Refs)

60. INDUCTION OF INDOMETHACIN SENSITIVE SUPPRESSOR CELLS (ISSC) BY CORYNEBACTERIUM PARVUM (C. PARVUM) AND THE EFFECT OF INTERLEUKIN-2 (IL-2) (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:957 1982

Studies were designed to determine whether increased prostaglandin production by these cells could account for this suppressed state. C parvum was injected IP or IV into C57BL/6 mice. After various intervals, the mice were sacrified, spleen cell suspension prepared and incubated with concanavalin A (Con A) with or without indomethacin (indo), an inhibitor of prostaglandin synthesis. In duplicate cultures, IL-2 was added. After 72 hours of incubation, the cultures, which were pulsed with 3H-thymidine, were harvested, radioactivity counted and % augmentation by indo or IL-2 calculated. Five to 7 days after IP injection of 350 ug C parvum, the reactivity of the spleen cells average 65.3 x 10(3) cpm/well which was augmented 77.9% by indo, as compared to control values of 104.9 x 10(3) cpm/well and 19.4% respectively. Significant augmentation by indo was seen by day 3, persisted past day 14 and was apparent with as little as 50 ug C parvum. When given IV, this agent was also effective in inducing suppression of Con A reactivity, averaging 39.5 x cpm/well, which was likewise enhanced by 91.4% by indo. When IL-2 was added simultaneously with indo, a further increase in Con A reactivity, averaging 30.1%, was seen. Often depressed proliferative responses were normalized by this combination. (no Refs)

61. CORYNEBACTERIUM PARVUM (CP) IMMUNOTHERAPY OF THE L5178Y CELL TUMOR DORMANT STATE IN DBA/2 MICE (MEETING ABSTRACT)

Baillargeon LM, Robinson MK, Schneiderman M, Wheelock EF
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Proc Am Assoc Cancer Res; 23:968 1982

The L5178Y cell tumor dormant state in DBA/2 mice is characterized by immunocompetence of the host and persistence of low numbers of tumor cells in the peritoneal cavity, making it ideal for evaluating immunotherapeutic regimens. CP was used for active non-specific immunotherapy and a CP double inoculation protocol developed which maximized cellular influx into the peritoneal cavity and cytolytic activity of the adherent peritoneal cells (AD-PEC). A peritoneal lavage was performed to enumerate the tumor burden in tumor dormant mice and to isolate tumor cells for use as targets in subsequent cytolytic assays. Mice were inoculated with 350ug CP on day 3 and day 10 after peritoneal lavage and were killed on day 19 at which time the PEC were assayed for endogenous tumor burden and AD-PEC cytolytic activity. Forty-seven percent of mice which received CP therapy were without detectable tumor cells, whereas 100% of PBS (phosphate-buffered saline)-treated controls contained tumor cells. The AD-PEC from mice that had no detectable tumor cells produced generally greater cytolytic activity in vitro when tested against their own previously isolated tumor cells than the AD-PEC from mice which remained tumor dormant. Small numbers of tumor cells were isolated from some CP treated mice that had a degree of AD-PEC cytolytic activity comparable to that in the PEC of tumor negative mice, thus supporting the validity of the negative tumor cell isolations from CP treated mice. The effector AD-PEC were characterized as macrophages by adherence to plastic, morphology, and resistance to anti-Thy 1.2 + C'. (no Refs)

62. CHANGES IN GLYCOSIDASE ACTIVITIES AND SURFACE LECTIN RECEPTORS OF GUINEA-PIG ALVEOLAR MACROPHAGES ACTIVATED BY CORYNEBACTERIUM PARVUM.

Blanquet PR, Scharfman A, Aerts C, Roussel P, Biserte G
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Cell Mol Biol; 28(1):111-118 1982

This report deals with the activity of five selected glycosidases and the topographic distribution of surface receptors of peroxidase-postlabeled Con A and four peroxidase-conjugated lectins in normal and Corynebacterium parvum-induced alveolar macrophages derived from guinea-pigs. It is shown that a striking rise in the activity of N-acetyl-beta-D-glucosaminidase, N-acetyl-beta-D-galactosaminidase, beta-D-glucuronidase and beta-D-galactosidase is paralleled by a more regular distribution of surface-bound wheat germ agglutinin in C parvum-induced cells. In contrast, the activity of alpha-D-mannosidase shows no increase; likewise, no apparent difference in surface staining patterns of Con A, soybean and Ricinus communis agglutinins is noted. (Author abstract) (26 Refs)

63. IMMUNOGENICITY, MACROPHAGE SENSITIVITY, AND THERAPEUTIC RESPONSE TO C. PARVUM OF FIBROSARCOMAS INDUCED IN C. PARVUM-TREATED AND UNTREATED MICE.

Woodruff M, Forbes G, Gordon J
Medical Res. Council, Clinical and Population Cytogenetics Unit, Western General Hosp., Edinburgh EH4 2XU, Scotland
Cancer Immunol Immunother; 12(3):255-258 1982

Tumors which developed after injection of methylcholanthrene (MC) to Corynebacterium parvum (CP)-treated mice or implantation of MC-impregnated discs in untreated mice were studied in adult (17-22 g) female mice of strains CBA and BALB/c. Origin and properties of tumors are presented. All the tumors tested showed some degree of sensitivity in vitro to the cytotoxic effect of CP-activated macrophages (Mphi) in effector-target cell ratios down to 5 :1; many were highly sensitive at these ratios and also showed varying degrees of sensitivity at a ratio of 2.5 : 1 (the lowest ratio tested). A 10-fold increase in the concentration of arginine in the medium made no significant difference to the score. No correlation between the therapeutic response of a tumor to CP in vivo and its sensitivity to CP-activated Mphi in vitro was observed, nor any evidence was noted that either of these parameters was influenced by repeated administration of CP during the period of carcinogenesis or by whether the carcinogen was administered in solution or as crystals on a Millipore disc. Tumors which developed after injection of a small (0.1 mg) dose of MC in mice given repeated injections of CP had a significantly higher immunogenicity index than those which developed in mice which did not receive CP. A suggestion of similar effect after the injection of 0.5 mg MC was observed, but the difference was not statistically significant. (7 Refs)

64. FURTHER STUDIES ON THE INHIBITION OF CHEMICAL CARCINOGENESIS BY CORYNEBACTERIUM PARVUM.

Woodruff M, Forbes G, Speedy G
Medical Res. Council, Clinical and Cytogenetics Unit, Western General Hosp., Edinburgh EH4 2XU, Scotland
Cancer Immunol Immunother; 12(3):259-265 1982

Effects of both single and repeated injection of Corynebacterium parvum (CP) on the incidence of fibrosarcoma in response to methylcholanthrene (MC) were studied in adult female (17-22 g) mice of strains CBA and BALB/c. The carcinogen was administered by sc or ip implantation of an MC-impregnated Millipore disc. In CBA mice, repeated iv injection of CP starting on day-4 (0.7 mg every 4 wk, or 0.35 every 2 wk) significantly delayed appearance of sarcomas after sc injection of 0.5 mg MC on day 0; repeated injection of CP starting on day 24, and a single injection of CP on day-4, 6, 20, or 28, had no significant effect. In BALB/c mice, repeated injection of CP starting on day-4 or +6 significantly delayed the appearance of sarcomas after sc injection of 0.25 mg MC, and some significant inhibition occurred even when repeated administration of CP was started on day 41. After implantation of a 5% MC-wax disc sarcomas developed in 8 of 8 untreated CBA mice but in only 13 of 21 CBA mice which received repeated iv injections of CP (0.35 mg every 2 wk starting on day-4, 6, or 20). In BALB/c mice sc implanted 0.5% MC-wax discs were extruded in 4 of 16 mice which received repeated iv injections of CP; in the remaining 12 mice sarcomas developed somewhat later than in untreated mice but the difference was not statistically significant. When MC-wax discs were implanted ip, repeated injections of CP from day-4 completely prevented the development of tumors, irrespective whether the disc was attached to the liver or elsewhere in the peritoneal cavity. Sc implantation of 0.1 mg MC discs resulted in the development of fibrosarcomas in nearly all untreated mice, and the time for tumors to develop was independent of the pore size of the disc. The pore size did, however, affect the response to CP. With discs of 0.22 micrometer pore size the development of sarcomas appeared to be somewhat delayed by repeated injection of CP starting before disc insertion, but the difference was not quite significant at the $P = 0.05$ level. (12 Refs)

CYTOKINE THERAPY

65. ACTIVATION OF HUMAN MONOCYTE-MEDIATED CYTOTOXICITY BY LIPOSOMES CONTAINING HUMAN LYMPHOKINE (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:1031 1982

The purpose of these studies was to determine whether human blood monocytes can be rendered tumoricidal following in vitro incubation with a lymphokine derived from peripheral blood mononuclear cells incubated with concanavalin (Con-A). We undertook these investigations because of the data demonstrating that appropriately activated macrophages are important in host defense against neoplasia. The multiple IV injections of liposomes containing lymphokines have been associated with regression of metastases in murine systems. We report here that human peripheral blood monocytes can be rendered tumoricidal in vitro following their interaction with a human lymphokine in either free form or encapsulated within multilamellar liposomes. Human monocytes incubated for 24 hr with human lymphokine contained within 100 nmol phospholipid resulted in the reproducible generation of cytotoxicity (50-70%) against A375 human melanoma cells at a 1:10 T/E ratio. Activation by liposome entrapped lymphokine was very efficient and required at least an 800 times lower concentration than the free unencapsulated lymphokine. We conclude that human monocytes can be activated by liposome entrapped lymphokine in vitro. Since the administration of free lymphokine in vivo may lead to the development of undesirable side effects, the ability to activate human monocytes by liposome-entrapped lymphokine may circumvent such consequences and thus have therapeutic potential. (no Refs)

66. RESTORATION OF ALLOGENEIC RESPONSIVENESS OF LYMPHOCYTES FROM CYCLOSPORIN A-TREATED ANIMALS WITH INTERLEUKIN 2.

Wang BS, Heacock EH, Zheng CX, Tilney NL, Mannick JA
Dept. Chemotherapy Res., Medical Res. Div., American Cyanamid Co., Lederle Laboratories, Pearl River, NY, 10965
Transplantation; 33(4):454-456 1982

The possibility that a defect at the helper cell level results in the inability to generate allocytotoxicity in cyclosporin A (Cy A)-treated mice was examined. The results indicated that the failure of alloreactivity resulted from the deletion or impairment of helper cells capable of producing interleukin 2 following Cy A treatment. Mechanisms by which Cy A may act on helper cells are discussed. (29 Refs)

67. ADOPTIVE CHEMOIMMUNOTHERAPY OF A SYNEGENEIC MURINE LYMPHOMA USING LONG-TERM LYMPHOID CELL LINES EXPANDED IN T-CELL GROWTH FACTOR: A NEW APPROACH TO CANCER IMMUNOTHERAPY (MEETING ABSTRACT)

Eberlein TJ, Rosenstein M, Rosenberg SA
Surgery Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD
Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

Recently techniques have been developed for the long term growth of cytotoxic T-lymphoid cells in vitro using T-cell growth factor (TCGF). We have investigated the use of these in vitro expanded T-cells for the immunotherapy of a disseminated syngeneic murine FBL-3 lymphoma. In this model, mice with disseminated tumor were treated on day 5 with 180mg/kg cytoxan and then 5 hrs later given lymphoid cells IP. In vivo immunized lymphocytes resulted in significantly improved survival in 3 of 3 experiments curing 53% of 38 animals compared to treatment with cytoxan alone (0 of 31 cured) or cytoxan plus unimmunized cells (0 of 40 cured). In vivo immunized lymphocytes were re-exposed to FBL-3 tumor in vitro for 5 days in complete medium (CM) or lectin-free TCGF (LF-TCGF). Adoptive transfer of both groups resulted in significantly improved survival in 6 of 6 experiments. Cytoxan cured 17% of 66 animals, cytoxan plus normal lymphocytes after IVS cured 6% of 47 animals. In vivo immunized cells resensitized in vitro to FBL-3 in CM or LF-TCFG cured 82% of 50 animals and 72% of 61 animals respectively. Cells from in vitro sensitization (IVS) were then expanded in LF-TCGF 7-10 fold. Adoptive transfer of immune lymphocytes resensitized to FBL-3 tumor in vitro and expanded in LF-TCGF conferred a significant survival benefit, curing 7 of 27 animals) compared to all controls. Again, in vivo immunized lymphocytes resensitized to FBL-3 tumor and expanded in LF-TCGF cured 56% of the animals with disseminated tumor, significantly prolonging survival over any control group. Clones were generated from IVS using limiting dilution techniques and when adoptively transferred also significantly enhanced survival. (no Refs)

68. LYMPHOTOXIN. AN IMMUNOLOGICAL HORMONE WITH ANTICARCINOGENIC AND ANTITUMOR ACTIVITY.

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Cancer Immunol Immunother; 12(3):181-190 1982

Anticarcinogenic and antitumor activities of lymphotoxin (LT), one of the immunologic hormones secreted by activated WBC, are reviewed. When 10(5) 104C1 guinea pig cells transformed by benzo(a)pyrene were mixed with lymphokine (LK) medium containing 150 units LT and the cells administered to a syngeneic guinea pig, the tumor outgrowth was retarded compared with untreated transformed cells. LK preparations probably contained a number of LK in addition to those that were measured. The variety of data suggests that one or more LK can by direct or indirect mechanisms inhibit tumor growth, although the identity, interrelationships, and comparative activities of the responsible LK remain to be established. The fourth class of cytotoxic LK is the LT. A number of forms or components ranging from approx 12,000-1,200,000 mol wt have been reported. LT can be produced by mitogen or antigen stimulation of WBC for periods ranging from 4-8 hr to 5-7 days. LT is generated by the culture of 10(7) lymphoid cells from lymph nodes, peripheral blood, spleen, or other WBC populations from humans or experimental animals for a period of 24 hr in serum-free medium with antigen or mitogen to activate the cells. Guinea pig and Syrian hamster LK can be produced with no detectable interferon (INF) activity. Hamster LK preparations induced by phytohemagglutinin (PHG), fetal bovine serum, Concanavalin A, or antigenic stimulation with key-hole limpet hemocyanin of peritoneal or spleen WBC contain no INF activity, with the LT units in the preparation varying over more than a 50-fold range. Biological activity of LT is in inducing an irreversible inhibition of carcinogen-induced morphological transformation in vitro. The anticarcinogenic activity of LT preparations is inhibited by galactose and PHG, indicating that the activity is due to LT. LT has a possible significance in preventive oncology, cancer therapy, and in general medicine and biology. (64 Refs)

THYMIC HORMONES AND OTHER IMMUNORESTORATIVE AGENTS

69. INCREASED SURVIVAL OF TUMOR-BEARING MICE AFTER ADMINISTRATION OF THYMOSIN PREINCUBATED SYNGENEIC BONE MARROW CELLS (MEETING ABSTRACT)

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Centre Paul Lamarque, Montpellier Cedex 34 033, France
Proc Am Assoc Cancer Res; 23:1017 1982

The present results are based on a system directly applicable to man, consisting of bone marrow transplants in C57Bl/6 mice with either methylcholanthrene induced tumor or Lewis tumor. Animals were treated by injection of syngeneic bone marrow cells from non-tumor-bearing mice. If these cells are preincubated in thymosin fraction 5 or alpha 1 before injection there is a significant retardation of tumor growth and metastatic disease followed by significantly increased survival time. In addition, we found that this action: 1) was T lymphocyte dependent and did not occur if bone marrow preincubated with thymosin was treated with anti-thy 1-2 serum; 2) was independent of NK activity. Mice treated with radioactive strontium showed no change for thymosin anti-tumor effects. Tumor bearing mice treated with CDDP (Cis-Platinum) or tumor local radiotherapy (16 grays) associated to thymosin preincubated bone marrow cells also demonstrated a significantly increased survival time as compared to mice treated by chemotherapy or radiotherapy alone. These results are sufficiently encouraging to warrant a randomized trial in order to evaluate the efficacy of administration of autologous bone marrow cells pretreated with thymosin after aggressive chemotherapy in the advanced solid tumor patient. (no Refs)

70. LOW SERUM THYMIC HORMONE LEVELS IN PATIENTS WITH CHRONIC GRAFT-VERSUS-HOST DISEASE.

Atkinson K, Incefy GS, Storb R, Sullivan KM, Iwata T, Dardenne M, Ochs HD, Good RA, Thomas ED

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Blood; 59(5):1073-1077 1982

We tested the hypothesis that chronic graft-versus-host disease (GVHD) is due to inadequate thymic function by examining pretransplant serum levels of facteur thymique serique (FTS). Four of five patients with no detectable FTS activity developed chronic GVHD, while one of four with some FTS activity did. Further patient numbers are needed to confirm or reject this hypothesis. We further postulated that chronic GVHD, whatever its cause, involves thymic epithelium as a target organ. When tested 11 mo or more posttransplant, patients with chronic GVHD had lower absolute FTS levels (p less than 0.02) and lower age-corrected levels (p = 0.05) than patients without chronic GVHD. Low values in chronic GVHD were associated with the disease itself and not its therapy. These findings show that thymic epithelial secretory function is impaired in chronic GVHD, and this may in part be responsible for the immunodeficiency characteristic of these patients. (Author abstract) (27 Refs)

71. POTENTIATION OF THE THYMOSIN IMMUNOREGULATORY EFFECT BY HYPOCORTICOIDISM IN RATS WITH DMBA-INDUCED CARCINOGENESIS IN MAMMARY GLANDS.

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Neoplasma; 29(1):19-27 1982

Effect of adrenalectomy and or thymosin administration on the tumor growth and immunity system were investigated on the models of 7,12-dimethylbenz(a)anthracene(DMBA)-induced mammary neoplasms in rats. Adrenalectomy and thymosin administration resulted in antitumorigenic action, whereas maximal inhibiting effect was achieved after thymosin injection in adrenalectomized animals. The maximal antitumorigenic effect of thymosin in adrenalectomized rats was accompanied by synergistic immunopotentiating effect of thymosin and adrenalectomy. Immunorehabilitation with thymosin and simultaneous correction of hormone production in the adrenal cortex are believed to enhance the effectiveness of therapy in cancer patients (Author abstract) (29 Refs)

ACTIVE SPECIFIC IMMUNIZATION

72. TUMOR VACCINE-INDUCED ANTITUMOR IMMUNITY ENHANCED BY ANTINEOPLASTIC AGENTS ELIMINATING SUPPRESSOR T CELLS (MEETING ABSTRACT)

Kataoka T, Akahori Y, Sakurai Y

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Proc Am Assoc Cancer Res; 23:999 1982

We showed previously that combination of L1210 murine leukemia cell vaccine and antineoplastic agents induced an enhanced L1210-specific antitumor immunity in histocompatible mice. In the present study we examined a role of antineoplastic agents in inducing the enhancement. Mice inoculated intraperitoneally (ip) with concanavalin A-bound L1210 vaccine twice at 1-week intervals were not refractory to subsequently ip inoculated 10(3) live L1210 cells. However, mice inoculated with the vaccine and further administered ip with mitomycin C (1.25 mg/kg) or cyclophosphamide (100 mg/kg) survived the inoculum of live L1210 cells. This enhanced antitumor immunity induction was inhibited when these mice were inoculated ip further with spleen cells of normal, unsensitized mice showing that antineoplastic agents potentiated the vaccine by eliminating spleen suppressor cells. These spleen cells in vitro treated with anti Thyl.2 antibody and complement did not inhibit the induction of enhancement indicating that T cells were associated with the suppression. Their inoculation before or on the day of, but not after, the second vaccination was suppressive suggesting that the transferred spleen cells suppressed the immune reaction inducible by the vaccination but not the effector phase occurring subsequently to live L1210 inoculation. Based on these findings we concluded that these antineoplastic agents eliminated spleen suppressor T cells in mice primed with the vaccine thereby making the second vaccination more effective resulting in induction of enhanced antitumor immunity. (no Refs)

73. ERADICATION OF MICROSCOPIC DEPOSITS OF LINE-10 HEPATOCARCINOMA IN THE LIVER BY ACTIVE SPECIFIC IMMUNIZATION (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:1015 1982

Guinea pigs with stage-II malignant disease were successfully treated by post-operative immunization with irradiated tumor cell vaccine. We tested the efficacy of this vaccine in eradicating line-10 cells in the organ of origin (the liver) to determine whether liver metastases were susceptible to active immunotherapy. Intraportal vein injection of line-10 cells in the strain-2 guinea pig resulted in growth of tumor foci in the liver, development of metastases in the hepatic lymph nodes and death with ascites. Growth of line-10 tumor foci could be prevented by immunization with an irradiated tumor cell vaccine containing cell wall of Mycobacterium bovis strain Bacillus Calmette-Guerin (BCG-CW) in an oil in water emulsion. Successful treatment required both line-10 tumor cells and BCG-CW emulsion; vaccines lacking either component were not effective. Immunization with irradiated line-one cells (a hepatoma antigenically distinct from line-10) did not prevent the outgrowth of line-10 cells. Active immunization was effective 1, 7 and 14 days after injection of line-10 cells. Animals rendered free of disease by vaccination rejected a challenge of line-10 cells, but not of line-one cells. This study has shown that active specific immunotherapy is an effective method for eradicating microscopic foci in the liver of a transplantable hepatocellular carcinoma. (1 Ref)

74. IMMUNOTHERAPEUTIC EFFECT OF TUMOR ANTIGENS EXTRACTED FROM A MURINE SARCOMA (MEETING ABSTRACT)

Inabe S, Pellis NR, Kahan BD
The University of Texas Health Science Center, Houston, TX, 77030
Proc Am Assoc Cancer Res; 23:1016 1982

Active specific immunotherapy (ASIRx) with isoelectrically purified tumor antigen following resection of a progressive neoplasm engenders resistance to recurrence and to challenge with an antigenically different fibrosarcoma. Treatment of syngeneic C3H/HeJ mice after resection of a 2 cm mass with weekly subcutaneous injections of 25ug of tumor antigen reduced mortality due to recurrence from 79% to 23%. The present study was initiated to determine the efficacy of (ASIRx) in decreasing the 46% recurrence rate following resection of a 1 cm MCA-F tumor and to assess the role of concomitant and de novo immune responses in the therapy induced increase in tumor resistance. SpC from mice displaying local recurrences following resection of 1 cm tumors facilitated in vitro tumor growth as evidenced by a 19.6% increase in 3HT uptake, while SpC from mice without recurrent tumor inhibited 3HT uptake by 20.5%. Following resection of 1 cm tumors, 80 mice were treated on postoperative days 1, 8 and 15 with 40 ug of MCA-F antigen. ASIRx induced in vivo resistance in mice otherwise destined for recurrence and converted the 20.5% facilitation to a 5.6% inhibition of 3HT uptake. On the other hand, therapy antagonized the protective result of concomitant immunity increasing the recurrence rate from 5 to 29% and completely abrogating the ability of SpC to inhibit in vitro tumor growth. Since the outcome of antigen specific therapy depends on the status of host immunity at the time of surgery an assay predictive of recurrence risk and of tumor immunity is essential to the timing and administration of ASIRx. (no Refs)

75. ANTIGENIC HETEROGENEITY OF THE GUINEA PIG LINE 10 HEPATOCARCINOMA. IMPLICATIONS FOR ACTIVE SPECIFIC IMMUNOTHERAPY.

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Cancer Immunol Immunother; 12(3):211-215 1982

Incidence of late tumor metastasis was examined in previously immunized inbred male Sewall Wright strain 2 guinea pigs and the factors contributing to the tumor recurrence were determined focusing on the relation of tumor relapse to the emergence of minor subpopulations of tumor cells that were less immunogenic than the parent tumor. Guinea pigs bearing L10 tumor could be cured of their systemic tumor burden by vaccination with x-irradiated L10 tumor cells admixed with BCG. All unvaccinated animals that received 10(6) L10 tumor cells by iv injection died from pulmonary tumors between 40-90 days after injection, with a median survival time of approx 65 days. When animals were treated with vaccine on days 1 and 8 following tumor induction, some of the animals died as early as controls, but the majority survived more than 180 days. Two animals, which had had been treated with vaccine and which survived more than 100 days, showed evidence of respiratory distress and were identified as presumptive late treatment failures. Two putative variant cell lines, L10-1 and L10-2, were isolated from their lymph nodes. Immune reactivity to the parent L10 and L10-1 was similar in all animals, whereas reactivity to L10-2 was significantly lower. Both the L10 parent and L10-1 were able to immunize and to elicit responses to the same extent. L10-2 was less antigenic in both the induction and the elicitation of immune responses. Results were compatible with the hypothesis that L10-2 expresses functionally less tumor-associated antigen. (32 Refs)

76. ACTIVE SPECIFIC IMMUNOTHERAPY OF GUINEA PIGS WITH VISCERAL TUMOR IMPLANTS.

Yarkoni E, Hunter JT, Sukumar S, Rapp HJ
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Cancer Immunol Immunother; 12(3):273-275 1982

Immunotherapeutic efficacy of the improved vaccine against established disseminated visceral micrometastases initiated by iv injection of L10 cells was studied in adult male Sewall Wright strain 2 guinea pigs. Vaccination with doses of 6.6 x 10(7) to 2 x 10(8) irradiated L10 (L10X) plus 5.4 mg heat-killed whole Mycobacterium phlei cells emulsion (M phlei KCE) given 7 and 14 days after iv tumor implantation led to survival of 90-100% of the treated animals for greater than 120 days. A lower dose of L10X was less effective. Immunization with doses of 1.8 or 5.4 mg M phlei KCE plus 2 x 10(8) L10X given 7 and 14 days after iv tumor inoculation produced survival of 90% of the treated animals whereas a dose of 0.2 mg of M phlei KCE plus 2 x 10(8) L10X did not produce a significant therapeutic effect. All animals treated with L10X alone died with pulmonary metastases within 62 days after iv tumor implantation. Immunization with doses of 4.4 x 10(7) or 13.2 x 10(7) L10X plus 3.6 mg heat-killed whole BCG cells emulsion (BCG KCE) given 7 and 14 days after iv tumor injection led to survival of 80-90% of the treated animals for greater than 120 days. Vaccine with doses of 1.2 or 3.6 mg BCG KCE plus 1.32 x 10(8) L10X given 7 and 14 days after iv tumor inoculation led to survival of 80-100% of the treated animals. Animals treated by injection of BCG KCE alone or with L10X alone, all died with multiple foci of pulmonary tumor within 56 or 71 days, respectively, after iv inoculation of L10 cells. (6 Refs)

SEROTHERAPY AND RELATED APPROACHES

77. PHASE I TRIALS OF EX-VIVO PLASMA PERFUSION WITH STAPH AUREUS COWAN STRAIN I (SAC) AND PROTEIN-A CHARCOAL (PACC) IN MALIGNANCY (MEETING ABSTRACT)

Messerschmidt G, Steis R, Dowling R, Parrillo J, Shelhammer J, Brown R, Herberman R, Maluish A, Phillips T, Voith M, Diehl L, Bowles C, Young RC, Glatstein E, Deisseroth A
National Cancer Institute, Bethesda, MD, 20205
Proc Am Soc Clin Oncol; 1:C-307 1982

Tumor regressions have been observed with immunoperfusion. We have treated 4 patients (pts) (8 procedures) with SAC and 4 pts (23 procedures) with PACC. With SAC 686-3517cc's plasma was infused, and with PACC 50-250cc's on an escalation protocol was infused. Toxicity was greater with SAC than PACC. Infusion of plasma perfused over SAC resulted in severe hypotension requiring volume expansion (8/8) and pressor administration (5/8) to maintain mean BP greater than or equal to 60mmHg. With PACC, aberrations in BP were not seen until doses of 200-250cc's were given and then only mild changes. Cardiac Index increased by greater than 100% with SAC. Only slight increases were seen with PACC at 200-250cc's and none below this level. Systemic vascular resistance (SVR) fell very low with SAC at the same time mean BP fell and cardiac index peaked. No changes in SVR have been seen with PACC. Mild to moderate hypoxia, hypocapnia, and tachypnea appeared to result directly from SAC therapy, but has not been seen with PACC therapy. WBC and platelet count fell by 50%+ within 4 hrs with SAC but not with PACC. Two pts died from cardio-pulmonary failure on treatment with SAC. No deaths have occurred with PACC. No changes in liver, renal, CNS, or GI (gastrointestinal) systems have been attributable to either therapy. Complement activation may explain the toxicity with SAC. No systemic complement activation has been shown with PACC. These patient trials show that cardio-pulmonary alterations can be severe as a result of immunoperfusion. These trials suggest toxicity is related to plasma dose. (no Refs)

78. IMMUNOMODULATION BY IFN-CONJUGATED MONOCLONAL ANTIBODY TO HUMAN OSTEOGENIC SARCOMA (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:1003 1982

Purified human lymphoblastoid interferon-alpha (IFN-alpha) has been coupled covalently, using N-succinimidyl 3-(2-pyridyldithio) proprionate (SPDP), to a mouse monoclonal antibody raised against the human osteogenic sarcoma cell line 791T. This antibody has been described elsewhere and binds specifically to cells of the immunizing tumor and to a number of other osteogenic sarcoma cell lines. The purified conjugate retains both antibody activity and IFN activity: binding to 791T cells can be shown in competitive binding assays using fluorescent-labelled antibody and the Fluorescence Activated Cell Sorter (FACS IV), and human peripheral blood lymphocyte-mediated lysis of 791T cells and the erythroleukemic cell line K562, is significantly enhanced after 1 hr incubation with effector cells. The antibody has been shown to localize in 791T xenografts in immunodeficient mice. The conjugate has been tested in an in vitro model system: in the presence of IFN-antibody conjugate bound to 791T cells, human NK cells exhibit significantly enhanced killing of a second, radiolabelled target (K562). Pre-incubation of mixtures of IFN and antibody with 791T cells failed to produce NK cell stimulation. This reagent represents a novel and potentially effective therapeutic tool which may allow specific targetting of IFN to the tumor site in vivo and subsequent activation of tumor-infiltrating NK cells. (1 Ref)

79. MONOCLONAL ANTIBODY THERAPY OF MURINE LEUKEMIA (MEETING ABSTRACT)

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Fred Hutchinson Cancer Research Center, Seattle, WA, 98104
Proc Am Assoc Cancer Res; 23:1045 1982

Monoclonal anti-Thy 1 antibody has induced prolonged survival and cure in a portion of treated animals. The purpose of the present study was to further quantify the effect and examine limiting factors. Mice were challenged with increasing doses of syngeneic AKR/J SL2 leukemia cells subcutaneously. Treatment with 100 ul ascites fluid (approximately 500 ug antibody) induced cure in 80% of animals challenged with 10(4) cells, 50% of the animals challenged with 10(5) cells and 0% of mice challenged with 10(6) cells. When a constant cell dose was administered followed by infusion of a single iv dose of antibody varying from 10 to 900 ul, prolongation of survival and cure were dose dependent with cure in all animals consistently achieved at the 900 ul but not 300 ul dose. Saturation was found to be dose dependent with complete saturation occurring following infusion of 900 ul but not 300 ul of ascites fluid. Despite the achievement of antibody saturation of all available Thy 1 sites on the tumor cells, growth of Thy 1 positive tumor cells continued. In contrast, antibody treatment with 100 or 900 ul of ascites fluid prevented the metastases of Thy-1 bearing leukemia cells. It did, however, permit the spread of tumor cell variants which did not express the target antigen. Thus, anti-Thy-1 antibody eliminated up to 3 x 10(5) leukemic cells in vivo. Limiting factors include the emergence of metastatic antigen negative variants, and the failure to eliminate antibody coated cells from solid tumors. (no Refs)

80. CHARACTERIZATION OF A MONOCLONAL ANTIBODY TO L1210 LEUKAEMIA.

Testorelli C, Morelli S, Goldin A, Nicolin A
NCI, NIH, Bethesda, MD, 20205
Br J Cancer; 45(3):395-402 1982

A mouse monoclonal cell line (L1) was produced by fusing the mouse myeloma P3X63/Ag8 with CD2F1 spleen cells immunized with a highly immunogenic subline of L1210 leukemia (L1210/DTIC). A very few positive clones (1%) were isolated and one of these was chosen for detailed study. The monoclonal antibody L1 is an IgM immunoglobulin strongly reacting in a complement-dependent cytotoxicity assay against L1210/Cr leukemia and its more or less immunogenic sublines. The specificity of the L1 antibody against L1210 leukemia was studied by extensive screening with normal adult and fetal tissues, lymphoid tissues from several independent strains and a panel of the most common experimental tumors, to all of which it was unreactive. Attempts at immunotherapy were carried out in DBA/2 mice challenged with L1210 leukemia and treated with L1 (ascites) and complement. Although the in vitro cytotoxic titer of ascites fluid from mice bearing hybridoma was very high (10(-7)), no therapeutic effect was obtained in vivo. (Author abstract) (29 Refs)

81. RADIOIMMUNOASSAY AND ANALYTICAL DETECTION OF HUMAN MAMMARY EPITHELIAL ANTIGENS (HME-AGS) IN BREAST CANCER PATIENTS USING MONOCLONAL AND POLYCLONAL SPECIFIC ANTIBODIES (MEETING ABSTRACT)

Ceriani RL, Sasaki M, Blank EW, Peterson JA
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Proc Am Assoc Cancer Res; 23:1078 1982

HME-Ags were quantitated in the sera of breast cancer patients at different stages in their disease and later identified in the same sera by sensitive analytical procedures. HME-Ags are normal differentiation antigens found in human breast epithelial cells be they normal or neoplastic. Polyclonal and monoclonal antibodies have been prepared against them recently by us. The competitive radioimmunoassay (RIA) was sensitive down to 10 ng/ml and the identification of HME-Ags in the sera was carried out by affinity chromatography, separation and identification steps. High levels of HME-Ags were found by radioimmunoassay in breast cancer patients with disseminated disease and in a percentage of those with primary breast cancers. Normal women, men and patients with disseminated cancer of non-breast origin were negative. In support of these findings, HME-Ags were identified by the polyclonal and monoclonal antibodies in the serum of those breast cancer patients with high RIA values for HME-Ags, thus demonstrating the specificity of the assay. While polyclonal anti-sera identified the already described HME-Ags monoclonal antibodies identified a breast epithelial specific antigen with a molecular weight of 45K. (1 Ref)

82. MONOCLONAL ANTIBODIES AGAINST AN ESTROGEN-REGULATED PROTEIN IN HUMAN BREAST CANCER (MEETING ABSTRACT)

Adams DJ, Edwards DP, McGuire WL
Department of Medicine, The University of Texas Health Science Center, San Antonio, TX, 78284
Proc Am Assoc Cancer Res; 23:920 1982

Recently our laboratory has identified an estrogen-regulated protein in the MCF-7 human breast cancer cell line using the double label ratio technique. This protein, termed 24K, migrates at 24,000 daltons on sodium dodecyl sulfate polyacrylamide gels, has a pI of 6.4, and represents about 1.6% of total incorporation into cytoplasmic protein following 6 days of estradiol stimulation of antiestrogen pretreated MCF-7 cells. The 24K response is dose dependent, specific for biologically active estrogens and parallels nuclear processing of estrogen receptor, suggesting that regulation of 24K is mediated via the estrogen receptor pathway in these cells. To quantitate estrogen regulation of the 24K protein, we have used ion exchange chromatography and gel filtration to obtain a partially purified preparation suitable for the generation of monoclonal antibodies with the hybridoma technique of Kohler and Milstein. These monoclonal antibodies are of the IgG1 subclass and can specifically immunoprecipitate 24K from radiolabelled MCF-7 cytosols. (no Refs)

83. IMMUNOHISTOLOGIC CHARACTERIZATION OF A MONOCLONAL ANTIBODY DIRECTED AGAINST SQUAMOUS CELL CARCINOMA OF THE LUNG (MEETING ABSTRACT)

Jothy S, Brenner B, Fuks A, Shuster J
McGill University, Montreal, Quebec, Canada
Lab Invest; 46(1):43A 1982

Various studies have demonstrated the usefulness of monoclonal antibodies in recognizing discrete tumor antigenic determinants. The present study describes the tissue reactivity of a monoclonal antibody prepared against a squamous cell carcinoma of the lung. The details of the preparation are fully described elsewhere. Briefly, the antigen was purified from a tumor extract by anti-beta2-microglobulin affinity chromatography and used to immunized mice. After hybridization with a mouse myeloma cell line and screening, the antibodies derived from the clones were tested by indirect immunofluorescence against various human tumors, normal tissues, and cell lines. With one clone, it was observed that three of three cases of squamous cell carcinomas of the lung demonstrated strong staining of the entire tumor islands. The staining was cytoplasmic with peripheral accentuation. Two of two cases of lung oat cell carcinoma were negative. Four of five cases of lung adenocarcinoma were negative. One case of adenocarcinoma which had areas of squamous differentiation was focally positive. One case of adenoid cystic carcinoma was positive. One case of adenoid cystic carcinoma was positive. Negative staining was observed with the following normal tissues: lung, liver, kidney, peripheral blood lymphocytes, colon, breast, with the following adenocarcinomas: colon and breast, and with melanoma. (no Refs)

84. MOUSE MONOCLONAL IGM ANTIBODY AGAINST HUMAN LUNG CANCER LINE SK-LC-3 WITH SPECIFICITY FOR H(O) BLOOD GROUP ANTIGEN (MEETING ABSTRACT)

Anger BR, Lloyd KO, Oettgen HF, Old LJ
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Hybridoma; 1(2):139 1982

Spleen cells from mice immunized with the human lung cancer line SK-LC-3 were fused with mouse NS-1 myeloma cells. One of the hybrid clones produced a monoclonal IgM antibody (designated F-3), detected with antimouse Ig-MHA and hemagglutination assays. This antibody was completely absorbed by O red cells and completely inhibited by low concentrations of H(O) glycoproteins and hog mucin (A+H). Bombay (Oh) red cells completely failed to absorb F-3 activity even after treatment with neuraminidase. A1, A2, A1B, A2B, and B red cells and A- and B-glycoproteins were less effective in absorbing or inhibiting F-3 activity. Other glycoproteins (including those having Lea or blood group precursor structures) showed little or no inhibitory activity. Serum from nude mice carrying F-3 hybridoma agglutinated O and A2 red cells at a titer of 1:40,000 and 1:640, respectively. A1, A1B, A2B, and B red cells were agglutinated with titers of 1:80 or less. Monoclonal antibody F-3 is, therefore, highly specific for H(O) blood group determinants. (no Refs)

85. A MONOCLONAL ANTIBODY USEFUL FOR THE DIFFERENTIAL DIAGNOSIS BETWEEN MALIGNANT LYMPHOMA AND NONHEMATOPOIETIC NEOPLASMS (MEETING ABSTRACT)

Battifora H, Trowbridge IS
City of Hope National Medical Center, Duarte, CA
Lab Invest; 46(1):8A 1982

The distinction between non-Hodgkin's lymphoma and undifferentiated nonlymphoid neoplasms may pose difficult problems even to experienced surgical pathologists. Adjunct studies such as electron microscopy and/or immunologic methods for the demonstration of cell surface or cytoplasmic globulins do not always resolve the diagnostic dilemma. A monoclonal antibody was raised against a human T cell leukemia line by conventional hybridoma techniques and designated as T29/33 and has been previously reported to recognize a major cell surface glycoprotein restricted to hematopoietic cells. This antibody was tested as a possible tool to distinguish non-Hodgkin's lymphomas from nonhematopoietic neoplasms. Forty lymphomas and 110 nonhematopoietic neoplasms of various types were studied by indirect immunofluorescent and indirect immunoperoxidase on cryostat frozen sections. Intense staining was observed on the cell membranes of all lymphomas. All of the control tumors gave negative results, but nonneoplastic lymphocytes in or around tumor cells stained strongly, thereby acting as an internal control. (no Refs)

86. IMMUNOHISTOCHEMICAL CLASSIFICATION OF NON-HODGKIN'S LYMPHOMAS USING MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

Borowitz MJ, Crocker BP
Department of Pathology, Duke University Medical Center, Durham, NC, 27710
Am J Clin Pathol; 77(2):247 1982

Immunologic classification of non-Hodgkin's lymphomas (NHL) usually has relied on analyzing suspensions of cells teased from tumors. This procedure requires special technics and may not yield a representative sample in some cases. Lymphocyte markers may also be detected on frozen tissue sections. We stained nine cases of HNHL by an indirect immunoperoxidase (IP) technic for SIg, and with monoclonal antibodies against Ia(HLADR), pan-T(0KT3,Leu1),T-Help(Leu3a),T-Sup(Leu2a,0KT8), and thymic (0KT6) antigens. Tumor cell suspensions also were studied in immunofluorescence and cytotoxicity. In four cases the suspensions contained mixed B and T cells; in section these had areas of tumor with partially preserved node. In three of these the tumors cells stained for SIg and/or Ia(B cell), while the fourth stained only with OKT3 and Leu3a. The remaining five cases were homogeneous and the section and suspension data agreed. These included two large cell lymphomas, one with both pan-T and Ia antigens; one CLL and one lymphoblastic lymphoma with identical T and thymic antigen phenotypes, and one B-lymphoblastic lymphoma. IP detection of lymphocyte surface antigens makes immunologic classification of HNHL more readily available in the pathology laboratory and is particularly useful in studying complex tumors with subtotal node involvement. (no Refs)

87. LOCALIZATION OF CARCINOMAS BY PHOTOSCANNING AND TOMOSCINTIGRAPHY AFTER INJECTION OF RADIOLABELLED MONOCLONAL ANTI-CEA ANTIBODIES (MEETING ABSTRACT)

Mach JP, Buchegger F, Berche C, Lumbroso JC, Forni M, Ritschard J, Haskell C, Girardet C, Schreyer M, Accolla R, Carrel S
Ludwig Institute for Cancer Research, Lausanne, Switzerland
Hybridoma; 1(2):186 1982

Monoclonal antibodies (Mabs) against specific epitopes of carcinoembryonic antigen (CEA), labeled with 131I and normal mouse IgG (polyclonal or monoclonal), labeled with 125I were injected into nude mice bearing grafts of human colon carcinoma and in patients with large bowel, pancreas or medullary thyroid carcinomas. In nude mice the tumor uptake as compared to all normal tissues ranged from 7 to 15 fold greater for Mabs and 1-4 for normal IgG, resulting in specificity indices ranging from 4-6. In patients, the tumors resected after injection showed a Mabs uptake ranging from 2 to 10 and specificity indices ranging from 2-7. Detection of 131I Mabs by standard photoscanning, helped by computerized subtraction of 99mTc labeled albumin, allowed the localization of 14 carcinoma in 28 patients. Detection of the same labeled Mabs by single photon emission computerized tomography (SPECT) allowed the localization of 16 tumor sites out of 17 studied in 17 other patients. The results indicate that the use of the most modern tool of immunology (Mabs) and of nuclear medicine (SPECT) improves the specificity and sensitivity of immunoscintigraphy. Furthermore, we think that such detections and the paired labeling experiments described, should be performed in nude mice and in patients with each new Mabs against solid tumors which are seriously considered for various forms of passive immunotherapy. Although no side effects were observed, we consider that these injections in patients should be restricted to strictly controlled scientific studies. (1 Ref)

88. DETECTION OF A HUMAN MELANOMA-ASSOCIATED ANTIGEN, P97, IN HISTOLOGICAL SECTIONS OF PRIMARY HUMAN MELANOMAS.

Garrigues HJ, Tilgen W, Hellstrom I, Franke W, Hellstrom KE

Program in Tumor Immunology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104

Int J Cancer; 29(5):511-515 1982

The unlabeled antibody technique of Sternberger was used to study the localization in histological sections of human melanoma-associated antigen p97, which is defined by a monoclonal antibody. The antigen was detected in 8 of 10 primary skin melanomas, in 6 of 7 metastatic melanomas and in 2 of 2 compound nevi. It was localized at the cell surface, the cytoplasm and the nucleus always being negative. The antigen was not seen in cells from three basal cell carcinomas, one squamous cell carcinoma, one leiomyosarcoma, or in samples of normal skin (including keratinocytes, connective tissue consisting of collagenous and elastic fibers, fibroblasts, sebaceous glands, blood vessels, smooth muscles, or inflammatory cells such as granulocytes, lymphocytes and macrophages), kidney or lung. There was, however, staining of some cells in the secretory segment of eccrine sweat glands from two patients, possibly corresponding to myoepithelial cells. Antigen expression was somewhat variable between cells from different melanomas as well as between individual cells from the same melanoma. The possible diagnostic value of this procedure for identification and classification of melanomas is discussed. (Author abstract) (24 Refs)

89. MELANOMA ASSOCIATED GLYCOPROTEINS DEFINED BY MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

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Hybridoma; 1(2):184 1982

Monoclonal antibody 9.2.27 has been used in biosynthetic enzymatic and structural studies to define an antigenic complex on human melanoma cells that consist of an N-linked glycoprotein (Mr 250,000) and a high molecular weight proteoglycan (HMW-C) with an Mr greater than 480,000. Pulse-chase biosynthetic analyses of the 250K glycoprotein indicated Endoglycosidase H-sensitive precursors. Biosynthesis of the HMW-C coincides with Endoglycosidase H resistance of the 250K glycoprotein and is inhibited by exposure of the melanoma cells to the ionophore monensin. Biosynthetic structural and enzymatic studies suggest that the 250K component recognized by the 9.2.27 monoclonal antibody is a core glycoprotein of a chondroitin sulfate proteoglycan found both in freshly explented melanoma tumor tissues and at the surface of cultured melanoma cells. Monoclonal antibody F11 recognizes a glycoprotein of Mr 100,000 (100K) in spent media of melanoma cells and three glycoproteins of Mr 75, 77 and 100K in detergent lysates of these same cells. Pulse-chase analyses indicate recognition of 75/77K molecules by F11 early in the chase in the absence of detectable 100K antigen and the kinetics of this analysis suggest that the 75/77K components may be biosynthetic precursors of the 100K glycoprotein. Treatment of melanoma cells with monensin prevents the biosynthesis of the 100K antigen resulting in the secretion of altered molecular weight species into spent media of melanoma cells. (no Refs)

90. MELANOMA AND GASTROINTESTINAL ADENOCARCINOMA ONCOFETAL ANTIGENS DEFINED BY MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

Steplewski Z, Herlyn M, Mitchell K, Herlyn D, Blaszczyk M, Koprowski H

The Wistar Institute, Philadelphia, PA, 19104

Hybridoma; 1(2):183 1982

Five groups of antigens were detected on the surface of human melanoma cells by a panel of 35 different monoclonal antibodies. In Group I, antigens were expressed only by melanoma cells. Group II antigens, detected by six monoclonal antibodies, are high molecular weight (MW) glycoproteins (260K and 290K). These antigens are expressed not only by melanoma cells, but also by other tumor cells of neural tube origin and by pigmented embryonal cells and represent the oncofetal protein group. Anti-melanoma monoclonal antibodies against group III antigens also bind to some lung carcinomas and one sarcoma, but do not bind to tumors of neural tube origin. Six anti-melanoma antibodies of Group IV bind to antigens with MW 85K and 120K and are also expressed on other tumors and on embryonal pigmented cells, but not on normal adult cells. In Group V, melanoma-associated antigens include DR-antigen and a group of antigens with different molecular sizes (79K, 119K and 139K) which are expressed on a variety of tumor cells, some embryonal cells, and some specialized normal cells. In gastrointestinal adenocarcinomas, monoclonal antibody-defined glycolipid antigens include a ganglioside containing sialylated lacto-N-fucopentaose II. This antigen is expressed in tumor cells and is detected in serum of patients with adenocarcinomas of stomach, pancreas and colon. The same antigen is present in meconium; thus, it is also an oncofetal antigen. Other anti-glycolipid monoclonal antibodies detect blood group B antigens, Lewisb antigen and a lacto-N-fucopentaose III. (no Refs)

91. IMAGE ENHANCEMENT IN IMMUNOSCINTIGRAPHY (MEETING ABSTRACT)

Perkins AC, Hardy JG, Whalley DR, Pimm MV, Farrands PA

Department of Medical Physics, Queen's Medical Centre, Nottingham, England

Nucl Med Communications; 3(2):122 1982

Radiolabelled monoclonal antibodies to tumor associated antigens have been investigated as radiopharmaceuticals for tumor localization. In general, the target-to-non-target (T:NT) ratios are too low for satisfactory gamma camera imaging. Dual-isotope imaging and background subtraction techniques are applied to enhance the T:NT ratios. Experiments have been undertaken using phantoms to optimize image enhancement. Iodine-131 was used to represent the antibody distribution and technetium-99m and indium-113m the activity in the non-tumor tissues. Both the technetium and the indium corrected images resulted in an enhancement of the T:NT ratio; the indium correction being the more appropriate for deep seated lesions. In vivo studies with radioiodinated anti-human tumor monoclonal antibody (791T/36) have been undertaken in immuno-deprived CBA mice bearing osteogenic sarcoma xenografts. Image enhancement resulting in T:NT ratios of up to 10:1 was achieved with both technetium-99m and indium-113m corrections. In humans with colorectal tumors uptake ratios of 8:1 have been obtained using the same monoclonal antibody. (no Refs)

92. DETECTION OF METASTATIC CARCINOMA USING MONOCLONAL ANTIBODIES (MEETING ABSTRACT)

Wraight EP, Lennox ES, Sikora K, Smedley HM

No affiliation given

Nucl Med Communications; 3(2):123 1982

Rat monoclonal antibodies (MCA) were prepared by immunizing rats with human colorectal carcinoma cell membranes and fusing splenic lymphocytes with a rat myeloma, Y3 Ag 1.2.3. Hybridoma supernatants were screened by binding assays on colorectal carcinoma lines. One hybridoma supernatant containing a monoclonal antibody with high binding activity was grown in large quantities in serum free medium. After ammonium sulphate precipitation the antibody was purified by ion-exchange chromatography. A modification of the chloramine-T method was used for iodination with I131. Binding assays to cell lines revealed that this coupling method left the biological activity and specificity of the monoclonal antibody substantially unaltered and significant tumor uptake was demonstrated after iv injection into xenograft bearing immune deprived mice. Five hundred uCi 131I MCA was injected into patients with metastatic colorectal and breast tumors. Scintigrams were obtained at 24 and 48 hours. Correction for activity in the blood pool and free iodine was attempted by injecting 99mTcO(4)- and 99mTc human serum albumin prior to imaging. Computerized substraction scans showed localized areas of high uptake corresponding well with areas of known disease. No clinical complications of this technique have been encountered and one patient has been scanned on two separate occasions without apparent problems. (no Refs)

93. MONOCLONAL ANTIBODIES TO TUMOR ASSOCIATED ANTIGENS (TAAS) ON TRANSITIONAL CELL CARCINOMA (TCC) (MEETING ABSTRACT)

Messing EM, Bubbers JE, Whitmore KE, DeKernion JB, Fahey JL

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association Missouri. American Urological Association 254 pp., 1982.

Murine monoclonal antibodies were separated to antigens on human TCC cells by fusion of spleen cells from mice recently immunized with TCC cells, with a non-secreting syngeneic myeloma cell line. Several such fusions have been performed. Immunoglobulin secreting hybrid cells which are immortalized and cloned have thus been created, so as to provide unlimited amounts of monospecific antibodies. Hybridoma supernatants have been screened for desired immunologic reactivity with: a) the immunizing cell line, b) other TCC cell lines, and c) malignant human cell lines of non-TCC origin, using a solid phase radioimmunoassay. Twenty-nine hybridomas produced antibodies to the immunizing lines: of these, 4 recognized calf serum (CS) or CS dependent antigens, 5 recognized common tissue antigens, and 16, while not reacting with all non-TCC cells, recognized antigens which failed to display the restricted expression expected of TAA. Four antibodies, however, were considered to be directed toward TCC TAAs since they recognized TCC cells only or most TCC cell lines and not more than 2 of 6 malignant non-TCC cells. Antibody 2E1-F3 which reacts with only (and all tested) TCC targets, was chosen for futher study. Quantitative absorptions of these antibodies with a panel of non-malignant homogenized tissue, (4 different organs from each of 4 patients) failed to reduce the ability of these antibodies to bind with TCC target cells, thus demonstrating that they did not react with normal human tissue. (no Refs)

94. MONOCLONAL ANTIBODIES OF HUMAN PROSTATE ACID PHOSPHATASE (MEETING ABSTRACT)

Lee CL, Li CY, Jou YH, Murphy GP, Chu TM
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Hybridoma-derived monoclonal antibodies directed to human prostate acid phosphatase (PAP) have been produced by fusing mouse myeloma cells (P3x63Ag8.653) with spleen cells from mice immunized with purified PAP. Supernatants of hybridoma cell culture were screened for antibody production by an immune hemolytic method, using PAP coupled to sheep red blood cells as target cells. Forty-nine percent (34/69) of hybrid clones were found to secrete anti-PAP antibodies. Four of these antibody-producing hybridoma cells were selected and further subcloned by limiting dilution method until only one single clone per well was obtained One hundred fifty-six out of 252 clones were found to continue secreting anti-PAP antibodies, which were subsequently classified into four different subclasses of immunoglobulin as IgM (3 clones), IgG2a (2 clones), IgG3 (1 clone) and IgG1 (150 clones) with Kappa-light chain. Four monoclonal antibodies, one from each isotype, were selected for characterization. Results from a direct binding assay suggested that hybridoma anti-PAP monoclonal antibodies IgG1 and IgM recognized two distinct epitopes of PAP molecule, while IgG2a and IgG3 antibodies recognized another (same) epitope. Immunologic specificity of these four monoclonal antibodies was further evaluated by a competitive binding assay and an immunohistochemical method. Results demonstrated that anti-PAP monoclonal antibodies IgG1 and IgM possessed a higher specificity for PAP than for other nonprostate acid phosphatases, in comparison with monoclonal antibodies IgG2a, IgG3 and xenoantibodies. (no Refs)

ANIMAL MODELS OF BIOLOGICAL THERAPY

95. MONOCLONAL ANTIBODY SEROTHERAPY OF SOLID TUMORS: A GUINEA PIG MODEL (MEETING ABSTRACT)

Bernhard MI, Foon KA, Clarke GC, Christensen L, Hoyer L, Key M, Hanna MG, Oldham RK
Biological Response Modifiers Program, National Cancer Institute,, Frederick Cancer Research Facility Frederick, MD, 21701
Proc Am Assoc Cancer Res; 23:1011 1982

The chemically induced, transplantable L10 hepatocellular carcinoma of strain 2 guinea pigs (gp) is a valuable model for tumor immunotherapy. Our aim is to investigate some of the possible immunotherapeutic applications of monoclonal antibodies and the L10 system appears particularly well suited to this purpose: (1) This model provides an autologous solid tumor with metastatic potential similar to solid tumors in man; (2) Immune responses in the guinea pig are analogous to those of man; and (3) Guinea pigs are exquisitely sensitive to anaphalytic shock, a consideration in cancer immunotherapy utilizing murine antibodies. Monoclonal antibodies were prepared to the L10 tumor and an IgG1 producing clone (D3) was selected for further study. The D3 antibody is a true monoclonal as assessed by 2 dimensional gel electrophoresis. Membrane immunofluorescence (FACS IV) demonstrated similar specificity. Immunoperoxidase assays on cryostat sections of tumor and normal tissue showed specific L10 tumor reactivity. Radioimmunoprecipitation of detergent extracts of L10 cells demonstrated the antigen on a polymeric molecule of 148,000 dalton unit size. Serotherapy trials using repeated injections of monoclonal antibody at widely varying dosages have produced significant reduction in tumor size without demonstratable side effects. Immunoperoxidase studies following monoclonal antibody infusion have shown specific localization of monoclonal antibody on primary and metastatic tumor. (no Refs)

CLINICAL IMMUNOLOGY

96. CIRCULATING IMMUNE COMPLEXES IN PATIENTS WITH METASTATIC BREAST CANCER (MEETING ABSTRACT)

Krieger G, Kehl A, Bause I, Kneba M, Nagel GA
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Proc Am Soc Clin Oncol; 1:C-9 1982

We report a prospective study designed to further evaluate clinical significance of circulating immune complexes (IC) as tumor markers and prognostic factors in patients (pts) with metastatic breast cancer (mbc). One hundred and ten pts with mbc are tested in 4 to 8 weekly intervals for the presence of serum IC using the C1q binding assay (Cba) and Raji cell radioimmunoassay (Rca). Results were correlated to prognostic factors and response to chemotherapy. Controls are 60 age matched healthy women and 71 pts with rheumatoid arthritis (RA). Currently the incidence of positive results (IC+) is 37% for pts with mbc, 56% for pts with RA, and 3% for healthy controls. Permanent IC elevation on repetitive measurements is found in 60% of the IC+ mbc pts. Mean IC levels are higher for mbc pts than for healthy controls but lower than for pts with RA. Results of Cba and Rca do not correlate in pts with mbc, in contrast to pts with RA. IC+ mbc pts differ from IC- pts in type of metastases (visceral metastases, IC+:52%, IC-:21%), menopausal status (prae- or peri- menopausal, IC+:56%, IC-:14%) and progressive disease (IC+:68%, IC-:39%). IC status does not predict chemotherapy responsiveness. Nine of 25 IC+ pts show a positive correlation between IC titers and change of tumor mass, 3 pts an inverse correlation (IC titers increase in remission). (no Refs)

97. STAGE-ASSOCIATED INCIDENCE OF SERUM CIRCULATING IMMUNE COMPLEXES IN PATIENTS WITH UNTREATED BRONCHOGENIC CARCINOMA.

Ruiz-Arguelles A, Jett JR, Ritts RE
(c/o Ritts) Microbiology Res. Lab., Mayo Graduate Sch. Medicine, Rochester, MN, 55905
Cancer Immunol Immunother; 12(3):197-201 1982

Immune complexes (IC) in serum samples from 46 untreated patients (23 males, 23 females, 37-80 yr old, mean age 60 yr) with bronchogenic carcinoma (BC) were quantitated by means of C1q-binding enzyme-linked immunosorbent assay, and results were compared with those obtained in healthy volunteers. Even though the levels of circulating IC were significantly higher in Stage III than in Stage I BC when analyzed as groups, if only positive patients are considered, the values found in patients between these groups were not statistically different. In 10 patients (5 in Stage I and 5 in Stage III), postoperative serum samples were analyzed for the amount of IC, and no significant differences were found as the result of the tumor removal or debulking within 4-7 days after surgery, nor was a significant difference observed in 5 more patients in whom a later sample at 15 days was studied. A qualitative association between the presence of IC and size of tumor, number of involved lymph nodes, metastasis, grade, cell type, age of patients, survival time, relapses and relapsing time (mean follow-up time was 37 mo, range 24-42 mo), time since onset of disease, and sex was evaluated and found to be negative in all instances. Neither the differences in frequency nor the levels of serum IC were significantly different from those between the granuloma and the nongranuloma patients when analyzed within the nonmalignant control group. Data indicated that the occurrence of IC has neither a prognostic value, as determined after analyzing the late outcome of the patients, nor a diagnostic one, since the incidence of IC in patients with nonmalignant thoracic diseases was found to be similar to that in the BC patients. (20 Refs)

98. RESPONSE OF PATIENTS WITH LUNG CARCINOMA TO PNEUMOCOCCAL VACCINE (MEETING ABSTRACT)

Mason BA, Dambra J, Dayal H, Schiffman G
Presbyterian-University of Pennsylvania Medical Center, Philadelphia, PA, 19104
Proc Am Soc Clin Oncol; 1:C-209 1982

A polyvalent vaccine of pneumococcal capsular polysaccharides has been licensed and released for prevention of infection caused by the prevalent invasive capsular serotypes. Included in the recommended target population are elderly adults, patients with chronic obstructive lung disease or altered immune status. Lung cancer patients have altered immunity and they may receive therapy which can suppress immune function. They are often elderly and have chronic lung disease. We vaccinated 62 lung cancer patients--33 receiving chemotherapy (CT), 24 had received prior radiation (RT), and 5 were surgical patients--and 23 age-matched controls. Antibodies to 12 of the 14 capsular types were measured by radioimmunoassay. Changes in antibody levels were compared for each serotype individually and also the composite scores computed from the geometric means of the 12 types. Comparisons among groups were performed by using non-parametric Kruskel-Wallis Test. Composite responses to the vaccine for the three groups showed CT to have a significantly inferior response to the vaccine compared to both the RT and control groups. The poor response of the CT may reflect the greater tumor burden or the direct toxic effect of chemotherapy and resultant impairment of humoral immunity in these patients. (no Refs)

99. AUTOLOGOUS IMMUNITY IN HUMAN COLORECTAL CANCER (CRC) (MEETING ABSTRACT)

Jessup JM, Babcock GF
The University of Texas System Cancer Center, M.D. Anderson Hospital and, Tumor Institute Houston, TX, 77030
Proc Am Assoc Cancer Res; 23:981 1982

Institution of effective immunotherapy for CRC depends upon the immune response by patients to autologous CRC. Tumor and histologically normal mucosa were enzymatically dissociated and cryopreserved in 7.5% DMSO (dimethyl sulfoxide) and 5% human serum albumin. These cells were assessed as targets for Humoral Antibody (HA) by indirect immunofluorescence, lymphocyte transformation in the mixed lymphocyte tumor interaction (MLTI), tumor cytostasis in a colony inhibition assay (CIA), and cutaneous hypersensitivity to intradermal injection of irradiated autologous tumor cells (T-DH) or mucosa cells (M-DH). Twelve of 17 patients with CRC had HA at titers of 1:8 which reacted with tumor but not mucosa either pre- or post- operatively. One of the 17 patients had HA to mucosa only. One of 9 patients developed T-DH, while 1 of 8 was positive in MLTI, and 3 of 10 were significantly cytostatic in the CIA. Two of 10 patients stimulated tumor colony formation. Seven patients were vaccinated with irradiated autologous cells and an adjuvant beginning 2 weeks after operation. Assessment of immune responses after 3 vaccinations revealed: 6 of 7 patients displayed T-DH without M-DH, 2 of 4 had MLTI, 5 of 6 were cytostatic in CIA, and all 7 had circulating HA. Combining all assays, immunotherapy significantly enhanced cell-mediated immunity to cryopreserved autologous tumor cells. The reactivity of HA also appeared to increase after immunotherapy. These results suggest that a complex interaction occurs in CRC between humoral and cellular immunity which may ultimately influence patient prognosis. (no Refs)

100. PROGNOSTIC SIGNIFICANCE OF IMMUNOLOGIC PHENOTYPE IN ADULT ACUTE LYMPHOCYTIC LEUKEMIA (ALL) (MEETING ABSTRACT)

Hurd DD, LeBien TW, Peterson BA, Kersey J, Gajl-Peczalska KJ, Bloomfield CD
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Proc Am Soc Clin Oncol; 1:C-481 1982

ALL in adults carries a poorer prognosis than in children, but some adult patients (pts) have long survivals. To determine if immunologic phenotypes would identify a good prognosis subgroup, we studied 49 newly diagnosed adults (32 male, 17 female) ranging in age from 15-75 years who were treated with standard intensive ALL induction chemotherapy. All 49 pts were studied for monotypic surface immunoglobulin (SIg) and sheep erythrocyte receptors (E). Eighteen pts were also studied for the common ALL antigen (CALLA) and 13 with a panel of monoclonal antibodies: BA-1, BA-2, HLA-DR (Ia), TA-1, OKT3, OKT9, OKT11/9.6, T101, OKM2. By standard lymphocyte surface markers, 5 pts were B (SIg+,E-), 11 T (E+,SIg-) and 33 non-B, non-T (SIg-, E-). Complete remissions (CR) were achieved in 76% non-B, non-T (N), 73% T and 20% B. CR durations were N, 2-96+ mos (median 22); T,1-36+ mos (median 8); and B less than 1 mo. Eight pts were CALLA+ (7 N, 1 B) and 10 were CALLA- (7 N,3 T). Among the N, there was no difference in CR rate (4/7 vs 5/7) or survival (median 10 vs 8 mos) for the CALLA+ or CALLA- pts. Marked phenotypic heterogeneity was seen among the 13 pts studied with the monoclonal panel. Only one recurring phenotype was seen; 5 pts (4 N,1 B) were Ia+,CALLA+,BA-1+, BA-2+ and negative with several anti-T cell monoclonal antibodies. The 4N patients survived 10-28 mos; the B pt survived 1 mo. The other 8 pts (5 N,3 T) had unique phenotypes and only 1 pt, with the following phenotype, survived more than 1 year: Ia-, CALLA-, BA-1-, TA-1+, E+ (37 mos). (no Refs)

101. IN SITU IMMUNOLOGIC PHENOTYPING OF MYCOSIS FUNGOIDES.

McMillan EM, Wasik R, Beeman K, Everett MA
Dept. Dermatology, Univ. Oklahoma Health Science Center, Oklahoma City, OK
J Am Acad Dermatol; 6(5):888-897 1982

In situ analysis of mycosis fungoides (MF) infiltrates with the use of monoclonal antibodies directed against T cells and T cell subsets in conjunction with the indirect immunoperoxidase technique is described. Punch biopsies were taken from six patients with MF. Two patients were affected by tumor stage MF and the remainder by plaque stage. The specificity and source of antibodies used are presented. In one patient with MF plaque stage, weak reactivity was observed with peripheral T cell antibodies, Leu 1, and OKT 3, in approx 50% of the cells. In three patients with plaque stage MF and one with tumor stage MF, a significant component of the dermal infiltrates (greater than or equal to 50%) was found to react positively with peripheral T cell antibodies Leu 1 and OKT 3. The results in the dermis with 'helper' antibodies Leu 3A and OKT 4 also indicated that a significant component of the populations reacted positively with these antibodies. Testing of the dermal infiltrates with 'suppressor' antibodies Leu 2 and OKT 8 gave a negative reaction in one patient and a positive reaction in a small number of cells in three patients. The majority of cells in the Pautrier abscesses stained positively with the peripheral T cell antibodies. Analysis with 'helper' antibodies gave a positive reaction in many of the cells constituting the abscesses. Testing with the 'suppressor' antibodies gave a negative reaction in the Pautrier abscesses in all three patients. Results in the positive control of tonsil were positive with all primary antibodies, with a predominantly interfollicular distribution of positive-reacting cells. Results with Leu 1 and OKT 3 indicate that a significant component of cutaneous infiltrating mononuclear cells of MF react with antibodies which normally detect mature T cell antigens. (33 Refs)

102. EVALUATION OF ASSAYS TO DETECT IMMUNE COMPLEXES AS AN IMMUNODIAGNOSTIC AID IN PATIENTS WITH MELANOMA.

Ruell P, Murray E, McCarthy WH, Hersey P

Medical Res. Dept., Kanematsu Memorial Inst., Sydney Hosp., Sydney, Australia

Oncodev Biol Med; 3(1):1-12 1982

Sera from 211 melanoma patients were tested before and after surgery for the presence of immune complexes (ic) by the 125I-C1q radioimmunoassay (C1q RIA) and a nephelometric monoclonal rheumatoid factor assay (mRhF). The patients were grouped according to stage of disease and therapy. Before surgery Stage III patients had a higher incidence of ic (26.9%) than Stage II (17.5%) and Stage I (6.1%) patients. The incidence of ic in the latter patients did not differ from that of normal controls. Stage I patients treated with BCG therapy had a higher incidence of ic before and after surgery to remove melanoma compared with untreated patients. The incidence of ic in Stage I and II patients was higher in sera taken after surgical removal of tumor compared to that in sera taken before surgery. Sequential studies revealed that ic often appeared then disappeared prior to clinical detection of recurrences. These results suggested that antigen excess was a frequent cause for failure to detect ic A prospective evaluation of the usefulness of assays for ic to monitor disease activity in melanoma patients was conducted. In some individual patients detection of ic was a prelude to recurrence from melanoma but the high false negative rate and the presence of elevated ic levels unrelated to recurrent tumor suggested that these assays should be of limited diagnostic value in the management of melanoma. (Author abstract) (23 Refs)

103. IMPAIRED IMMUNOCOMPETENCE IN PATIENTS WITH MALIGNANT GLIOMAS: THE POSSIBLE ROLE OF TG-LYMPHOCYTE SUBPOPULATIONS.

Gerosa MA, Olivi A, Rosenblum ML, Semenzato GP, Pezzutto A, Mahaley MS, Salcman M

Instituto di Neurochirurgia, Universita di Padova, Padua, Italy

Neurosurgery; 10(5):571-573 1982

T suppressor (Tg) and T helper (Tm) cells were analyzed in peripheral blood from 10 patients with malignant astrocytoma and 6 with glioblastoma multiforme (7 men, 9 women; 18-71 yr old) as measures of immunocompetence. Tg and Tm cells were detected using IgG- or IgM-coated ox RBC, respectively. Mean percentage of Tm lymphocytes was considered normal both pre- and postoperatively. However, Tg cells were significantly increased preoperatively as compared to 16 normal controls (18.55 +-1.11 vs 12.72 +-1.19, p less than 0.001), and a slight increase was observed after surgery and radiation therapy. There were no significant differences between the two types of gliomas. The postoperative reduction may be related to chemical- or radiation-induced immunosuppression. The increased numbers of Tg cells found in these patients may correlate with the previously reported impairment of immunocompetence in these brain tumor patients. (17 Refs)

104. FUNCTIONAL PROPERTIES OF NATURAL KILLER CELLS IN CARCINOMA OF THE PROSTATE (MEETING ABSTRACT)

Wirth MP, Schmitz-Drager BJ, Ackermann R

No affiliation given

77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

Natural killer (NK) - cells are believed to participate in the immunological defense of malignant tumors. Earlier experiments have shown a reduced spontaneous cell-mediated cytotoxicity (SCMC) in patients with advanced carcinoma of the prostate (CaP). Aim of this study was to investigate reasons for the depressed SCMC in advanced CaP. SCMC was determined in a 51Cr-release assay with peripheral mononuclear cells (PMC) from 5 patients with localized CaP, 8 patients with advanced CaP and 5 healthy male donors. Mononuclear cells from regional tumor-draining lymph nodes of 4 patients with localized CaP and 4 tumorfree patients were examined for their SCMC. Various tumor cell lines originating from CaP and other tumors served as target cells. Functional properties of NK-cells were analyzed by stimulation with human interferon-beta (IFN-beta). The experiments revealed a significant increase of SCMC following IFN-beta stimulation even in patients with advanced CaP indicating the normal function of peripheral NK-cells in these patients. The reduced SCMC in advanced CaP may be explained by a diminished number of mature NK-cell or by inhibitory mechanisms. IFN-beta stimulation did not improve the reactivity of mononuclear cells from tumor-draining lymph nodes of patients with localized CaP, whereas nodal mononuclear cells from tumorfree patients responded to IFN-beta stimulation. This finding is indicative for a disorder of NK-cells in the tumor-draining lymphatic system in patients with CaP. (no Refs)

105. THE MEASUREMENT OF LEUKOCYTE SUBSETS IN THE PERIPHERAL BLOOD OF CANCER PATIENTS WITH SOLID TUMORS USING MONOCLONAL ANTIBODY REAGENTS.

Harris JE, DeBoer KP, Vahey AL, Braun DP
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Med Pediatr Oncol; 10(2):185-194 1982

Monocyte and lymphocyte subsets were quantitated in the peripheral blood of normal subjects and patients with solid tumors using the monoclonal antibody reagents OKM1, BRL63D3, OKT3, OKT4, and OKT8. Percentages and numbers of cells reacting with monoclonal reagents were analyzed by indirect immunofluorescence. Correlations between leukocyte subset values and stage of disease or immunocompetence were sought. No differences from normal were seen in the percentage of OKT3, OKT4, and OKT8 cells or in the ratios of OKT4/OKT8 cells in peripheral blood mononuclear cells (PBMC) from all cancer patients, patients with localized disease, or patients with advanced disease. A significant decrease in absolute numbers of lymphocytes, OKT3 cells, OKT4 cells, and OKT8 cells was seen in the peripheral blood of patients with advanced disease reflecting the absolute lymphopenia of these patients. A significant increase was seen in the percentages of PBMC reacting with OKM1 and BRL63D3 from patients with advanced disease compared with normal donors of localized disease patients. A positive correlation was found between PHA responsiveness and absolute numbers of OKT3 and OKT4 cells. A negative correlation was found between PHA responsiveness and percentages of OKM1 cells. These data indicate that malignant disease does not alter T cell subset percentages in patient peripheral blood but may decrease their absolute numbers in association with absolute lymphopenia. On the other hand, percentages of OKM1 and BRL63D3 cells are increased in patients with advanced solid tumors in association with impaired PHA responsiveness. (Author abstract) (19 Refs)

106. EFFECTS OF INTERFERON THERAPY ON MONOCYTE FUNCTIONS OF CANCER PATIENTS (MEETING ABSTRACT)

Cianciolo G, Brenckman W, Snyderman R
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Proc Am Assoc Cancer Res; 23:950 1982

The effects of interferon therapy on monocyte function in humans with cancer have not been well characterized but this agent has been reported to enhance phagocytic activity of macrophages both in vivo and in vitro. Studies were therefore performed on seventeen ambulatory patients with cancer who were being treated with varying doses of human lymphoblastoid interferon. The study design utilized single and repeated (15 over 5 weeks) incremental doses of interferon ranging from 0.1 to 7.5 megaunits/m2. Four monocyte functions were studied: 1) chemotaxis and 2) morphological polarization to oligopeptide chemoattractants or zymosan activated human serum, 3) phagocytosis of 51Cr-labeled opsonized sheep erythrocytes (SRBC) and, 4) production of superoxide anion in response to phorbol myristate acetate (PMA). Patient values were compared to mean values obtained from 67 healthy volunteers tested during the same time period. Monocyte chemotactic responsiveness and polarization were depressed in 30 and 56% respectively of the cancer patients prior to the start of therapy and remained so (38 and 56% respectively) during and after treatment. Phagocytosis of SRBC was normal before therapy and was not affected by interferon treatment. The ability to produce superoxide anion was elevated in 54% of the patients before treatment and increased slightly to 62% after therapy. There were no discernible trends from pre-therapy values for any of the individual patients. (no Refs)

107. IMMUNOLOGICAL MONITORING OF PATIENTS RECEIVING RECOMBINANT LEUKOCYTE A INTERFERON (MEETING ABSTRACT)

Maluish AE, Ortaldo JR, Sherwin S, Leavitt R, Strong DM, Fine S, Wiernik P, Oldham RK, Herberman RB
Uniformed Services University of the Health Sciences, Bethesda, MD, 20014
Proc Am Soc Clin Oncol; 1:C-153 1982

One hundred patients receiving recombinant leukocyte A interferon (IFN) in 2 phase-1 studies were evaluated to determine the effect of IFN on immune function. Interferon was given by intra-muscular injection either twice daily or three times weekly for 28 days with groups of 5 patients receiving one of several doses of IFN. Doses ranged from 0.5-100 million units IFN. The studies were designed to determine the maximum tolerated dose (presented separately) and the optimum immunomodulatory dose. Blood specimens were obtained 2 or 3 times prior to the start of treatment to establish the baseline reactivity in easy assay. Seven to eight specimens were obtained during the course of treatment. Natural cytotoxicity (NK) was measured in a 4-hour 51Cr-release assay. NK activity did not show any significant or sustained elevation at any dose of either protocol. In fact, there was a trend towards a depression of NK activity in many patients. Preliminary determinations of monocyte function by a growth inhibition assay show a consistent and sustained elevation in some patients. In addition to NK and monocyte function assays, lymphoproliferative responses to concanavalin A and allogeneic mixed leukocytes were measured. Enumeration of lymphocyte subpopulations, performed by immunofluorescence staining with monoclonal antibodies and analysis by flow cytometry showed some elevation in OK T10 positive cells. These data and their correlation with the functional data will be discussed. (no Refs)

108. SERIAL CHANGES IN CIRCULATING IMMUNE COMPLEXES (CIC) IN PATIENTS WITH METASTATIC CANCER AFTER A SINGLE PLASMA EXCHANGE (MEETING ABSTRACT)

Edelstein R, Lima F, Levy C, Israel L, Baudelot J, Samak R
Oncology Department and Transfusion, University of Paris XIII, 93000 Bobigny, France
Proc Am Assoc Cancer Res; 23:1012 1982

Levels of CIC were determined serially in 8 patients with various metastatic cancers 1 hour before and 1 hour, 1, 2, 4 and 7 days after a single exchange of 0.56 to 2.89 liters of plasma. CIC were quantitated by measuring polyethylene glycol precipitated C4 and expressed as a percentage of total serum C4. All serum samples were assayed 'blind'. Prior to plasma exchange 4 out of the 8 patients had elevated CIC. The pre-exchange level in these 4 patients was 18.5 +/-4.8%. CIC levels dropped within the normal range immediately after plasma exchange. As early as 24 hours post-exchange, CIC levels began to rise and had returned to baseline levels by day 4 post-exchange. Of the 4 patients who did not have initially high levels, one patient had no detectable immune complexes at any stage (0% throughout) and the other 3 patients (pre-exchange levels, 10 %, 10 % and 11 %) exhibited similar kinetic profiles to those of patients with initially elevated levels (rapid clearance followed by rapid reapparance of CIC). The rapid renewal of CIC following plasma exchange indicates that effective and lasting clearance of potentially immunosuppressive CIC from the circulation of patients with cancer cannot be achieved with a single plasma exchange nor probably with any other single procedure, and that frequent and repeated procedures would probably be required. (no Refs)

REVIEWS

109. IMMUNOLOGICAL MECHANISMS OF GRAFT-VERSUS-HOST DISEASE IN MAN.

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Transplantation Biology and Clinical Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Transplantation; 33(5):459-464 1982

Immunological studies in clinical graft-versus-host disease (GVHD) and associated phenomena, such as autoimmunity, immunodeficiency, and immune dysfunction are reviewed. Despite the restriction of donor-recipient pairs to human leukocyte antigen-identical siblings and the use of postgrafting methotrexate or cyclosporin A, acute GVHD occur in 30-50% of patients with successful allogeneic bone marrow transplantation (BMT). In 5-10% of all cases, GVHD is associated with fatal complications. Chronic GVHD affects 25-30% of patients surviving for greater than 180 days after transplantation. Humoral immunity is thought to be less important than cellular immunity in GVHD. Articles on the relationship of humoral immunity to GVHD are reviewed. Peripheral T cell profiles in marrow-grafted patients indicate that abnormalities of T cell maturation and imbalance of T cell subset development are not related to GVHD but rather to conditions prevalent after BMT. Lymphocyte proliferative responses in GVHD patients are described. Nonspecific cytotoxicity has been observed in GVHD. The roles of cytotoxic, natural killer, and suppressor T lymphocytes in GVHD are considered. Immunodeficiency is common in patients following BMT. Later, patients without GVHD recover their immune function, while those with chronic GVHD remain immunologically impaired. Aberrations of immune regulation are associated with chronic GVHD. (66 Refs)

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CLINICAL CANCER IMMUNOLOGY AND IMMUNOTHERAPY

SERIES CT06 No. 82/11

NOVEMBER, 1982

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CLINICAL TRIALS

1. COMBINATION CHEMOTHERAPY PLUS BCG IN THE TREATMENT OF DISSEMINATED MALIGNANT MELANOMA: A SOUTHWEST ONCOLOGY GROUP STUDY.

Costanzi JJ, Al-Sarraf M, Groppe C, Bottomley R, Fabian C, Neidhart J, Dixon D
MW 414, Univ. Texas Medical Branch, Galveston, TX, 77550
Med Pediatr Oncol; 10(3):251-258 1982

The Southwest Oncology Group performed a randomized study comparing combination chemotherapy alone vs combination chemotherapy plus BCG vs dacarbazine plus BCG in the treatment of disseminated malignant melanoma. A 31% response rate was noted with combination chemotherapy alone, a 27% response rate with combination chemotherapy plus BCG, and an 18% response rate with DTIC plus BCG. Survival was not influenced by type of therapy, but the responders had significantly longer survival than the nonresponders. There appeared to be some significant differences in response as related to age wherein those patients between the ages of 30 and 60 yr had a higher response rate to combination chemotherapy as

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compared to DTIC plus BCG. Those patients older than 60 yr of age had a higher response rate in the BCG groups. Furthermore, in those patients older than 60 yr of age who responded, their duration of response was longer if they received BCG than those who did not receive BCG. It should be emphasized that those differences noted in various age groups could occur by chance alone. These differences should be studied in the future. by appropriate pretreatment stratifications. Patients with higher peripheral lymphocyte counts had significantly better response rates and those patients with higher numbers of positive delayed hypersensitivity skin tests had significantly greater survival. A significant improvement in survival was noted in patients whose PPD converted from negative to positive during therapy. (Author abstract) (11 Refs)

2. LIMITED SQUAMOUS CELL CARCINOMA OF THE LUNG: A SOUTHWEST ONCOLOGY GROUP RANDOMIZED STUDY OF RADIATION WITH OR WITHOUT DOXORUBICIN CHEMOTHERAPY AND WITH OR WITHOUT LEVAMISOLE IMMUNOTHERAPY.

White JE, Chen T, Reed R, Mira J, Stuckey WJ, Weatherall T, O'Bryan R, Samson MK, Seydel HG
Southwest Oncology Group, Operations Office, c/o Cancer Treatment and Res. Center, 4450 Medical Dr., San Antonio, TX, 78229
Cancer Treat Rep; 66(5):1113-1120 1982

In 1976, the Southwest Oncology Group activated a four-arm randomized study of limited squamous cell carcinoma of the lung. The purpose of this study was to determine if doxorubicin and/or levamisole added to radiation therapy improved the local control rate and survival in patients with limited squamous cell carcinoma of the lung. Of the 107 eligible patients, 15 (14%) had complete responses and 20 (19%) had partial responses. When compared by chemotherapy, immunotherapy, and performance status, no statistically significant difference was found in response rates or in survival. Although not statistically significant, the survival and response rates of patients in the combined levamisole arms were shorter than those of patients in the combined arms not containing levamisole. Patients receiving radiation therapy alone had the best survival. The irradiated field was the site of failure in 68 (88%) of the 77 patients in whom the site of failure was specified. Fifty (65%) of the patients failed in the radiation therapy field only. Chemotherapy and/or immunotherapy as employed in this protocol were of no benefit. (Author abstract) (33 Refs)

3. CHEMOTHERAPY VERSUS CHEMOIMMUNOTHERAPY WITH LEVAMISOLE OR CORYNEBACTERIUM PARVUM IN ADVANCED LUNG CANCER.

Chahinian AP, Goldberg J, Holland JF, Reisman A, Jaffrey IS, Mandel EM
Dept. Neoplastic Diseases, Mount Sinai Sch. Medicine, 1 Gustave L. Levy Pl, New York, NY, 10029
Cancer Treat Rep; 66(6):1291-1297 1982

A total of 109 patients with advanced lung cancer, all cell types, were randomized between MACC chemotherapy only, consisting of methotrexate, doxorubicin (Adriamycin), cyclophosphamide, and lomustine (CCNU); MACC plus levamisole (LMS) orally; and MACC plus Corynebacterium parvum (CP) sc. Of these patients, 101 were evaluable, with no differences among the three treatment groups for overall response rate and survival time. Objective response rates and median survival times were 41% and 230 days for patients given MACC only, 39% and 257 days for those given MACC plus LMS, and 44% and 223 days for those given MACC plus CP, respectively. There was a significant increase in survival for patients with large cell anaplastic carcinoma receiving CP or LMS, particularly in the good-performance-status category. Pretreatment delayed cutaneous hypersensitivity to recall antigens in 50 patients had prognostic significance, but repeat tests after 2 months of treatment in 30 patients did not show different patterns of conversion among the three groups. There was no difference in hematologic toxicity among the three groups. With the possible exception of large cell anaplastic carcinoma, immunotherapy with LMS or CP as given in this trial does not appear to be therapeutically advantageous in advanced lung cancer. (Author abstract) (24 Refs)

4. COMBINATION CHEMOTHERAPY-RADIOTHERAPY WITH AND WITHOUT THE METHANOL-EXTRACTION RESIDUE OF BACILLUS CALMETTE-GUERIN (MER) IN SMALL CELL CARCINOMA OF THE LUNG. A PROSPECTIVE RANDOMIZED TRIAL OF THE PIEDMONT ONCOLOGY ASSOCIATION.

Jackson DV, Paschal BR, Ferree C, Richards F, Muss HB, Cooper MR, White DR, Stuart JJ, Spurr CL, Wells B, Sartiano G, McFarland J, McCulloch J
Bowman Gray Sch. Medicine, Wake Forest Univ., South Hawthorne Road, Winston-Salem, NC, 27103
Cancer; 50(1):48-52 1982

The effect of addition of the nonspecific immunostimulant, MER, to combined treatment with chemotherapy and radiotherapy in small cell carcinoma of the lung was evaluated in a prospective randomized trial involving 102 evaluable patients. Chemotherapy consisted of cyclophosphamide, Adriamycin, vincristine, methotrexate, and lomustine; and radiotherapy was administered to the primary lesion, mediastinum, supraclavicular areas, and whole brain. Of 47 patients administered MER 400 mcg intradermally every 6 wk, 12 (26%) attained complete remission with a median survival of 22.9 mo. Complete remission was observed in 17 (31%) of 55 patients who received no MER with a median survival of 20.0 mo (p greater than 0.05). Survival greater than or equal to 2 yr has been observed in five patients who received MER and two patients who did not receive MER. The response rate and duration, survival, and toxicity of the two treatment arms were similar with the exception of cutaneous and occasional systemic reaction to MER. MER as used in this study has not influenced the overall results of a combined modality treatment program for patients with small cell carcinoma of the lung. (Author abstract) (13 Refs)

5. INTERFERON THERAPY IN JUVENILE LARYNGEAL PAPILLOMATOSIS.

Haglund S, Lundquist PG, Cantell K, Strander H
Dept. Otolaryngology, Karolinska Sjukhuset, S-104 01 Stockholm 60, Sweden
Arch Otolaryngol; 107(6):327-332 1981

Seven cases of severe juvenile laryngeal papillomatosis were treated with exogenous leukocyte interferon (IFN-alpha). Tumor progression occurred in all cases before treatment. During treatment, the tumors decreased in size. When treatment was discontinued (5 cases), tumor growth recurred, and after restarting therapy, the tumors once more decreased in size. In one case, the tumor completely vanished. In another case with extensive papillomatosis that extended up to the base of the tongue, a tracheostomy could be closed with only a thin mass of papillomatous tissue that remained on the vocal cords. Exogenous leukocyte interferon therapy can affect the clinical course of juvenile laryngeal papillomatosis. The optimal schedule for therapy has yet to be determined. (Author abstract) (25 Refs)

6. IMMUNOSTIMULATION WITH VITAMIN A IN ADVANCED CERVICAL CARCINOMA.

Kucera H, Micksche M
I. Univ.-Frauenklinik, Spitalgasse 23, A-1090 Wien, Austria
Fortschr Med; 100(16):760-763 1982

Treatment of advanced, inoperable cervical carcinoma with vitamin A palmitate (VAP) and radiotherapy (RT) was studied. Twenty-one women received VAP and RT; 21 received only RT. In response to phytohemagglutinin increased blastogenic response was found in 66% of those receiving VAP and RT and 33% of those receiving only RT. VAP evidently affects T-cell response. Patients receiving VAP had an insignificantly lower rate of relapse than those receiving only RT. Further studies of VAP are warranted. (20 Refs) (In GER)

7. PORCINE SENSITIZED LYMPH NODE CELLS (IMMUNOTHERAPY) AND ATTENUATED IRRADIATION FOR INFILTRATIVE TRANSITIONAL CELL CARCINOMA OF BLADDER.

Cockett AT, Di Sant'Agnese PA, Hamlin DJ, Keys HM
601 Elmwood Ave., Rochester, NY, 14642
Urology; 19(6):593-598 1982

Thirty-four patients with infiltrative bladder carcinoma, Stage B2C or higher were treated with immunotherapy and irradiation. Seventeen patients are alive, and 17 have succumbed to their disease. Eight patients underwent cystectomy after immunotherapy and irradiation; 6 of 8 are alive and well at the present time. The technique of immunotherapy is outlined. New methodology for sequential CT scans and scheduled bladder biopsies is mentioned. The 17 patients have survived 12 to 69 mo after immunotherapy and irradiation. Downstaging is demonstrated based on sequential CT scans of the bony pelvis and histologic biopsy. The biopsies reveal eosinophilia and multinucleated giant cells, a specific response to immunotherapy. A prospective randomized study will be initiated. (Author abstract) (10 Refs)

8. NEUTROPHIL-MEDIATED TUMOR CELL DESTRUCTION IN CANCER ASCITES.

Katano M, Torisu M
(c/o Torisu) Div. Clinical Immunology, Dept. First Surgery, Kyushu Univ. Sch. Medicine, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812, Japan
Cancer; 50(1):62-68 1982

Intraperitoneal injections of OK-432, originated from Group A streptococcus pyogenes of human origin, were administered to 77 patients with ascites caused by cancer of the digestive tract. Complete disappearance of effusion was observed in 43 cases, its reduction in 5 out of 77. They received cytologic examination of ascites daily before and after OK-432 injection. One of these patients, a 77-yr-old man with carcinomatous peritonitis due to gastric cancer, showed an interesting phenomenon after OK-432 injection. All adenocarcinoma cells in his ascites disappeared at least within 36 hr after OK-432 injection with increasing number of intraperitoneal neutrophils. In addition, neutrophils collected from his ascites or peripheral blood showed cytostatic effect on his ascites-derived tumor cells in vitro. His neutrophil-depleted intraperitoneal cells, however, had no significant effect on DNA synthesis of his tumor cells in vitro. OK-432 itself had no significant effect on DNA synthesis of his tumor cells in vitro. This report describes a patient in whom OK-432-induced neutrophils may play an important role in his tumor cell destruction in ascites. (Author abstract) (11 Refs)

INTERFERON

9. SENSITIVITY AND RESISTANCE OF HUMAN TUMOUR CELLS TO INTERFERON AND RINRCN.

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Nature; 297(5865):417-419 1982

The antiproliferative effects of interferon (IFN) and double stranded (ds)RNA on human HT1080 fibrosarcoma and RT4 epidermal carcinoma cell lines were characterized using Luria-Delbruck fluctuation analysis of IFN resistance (IFNr). Examination of isolated colonies derived from resistant populations revealed that IFNr cells possess the same population doubling times in the presence and absence of IFN at concentrations normally resulting in complete cessation of growth. Consistent with the idea that IFNr is an induced trait, resistant colonies reverted to a sensitive state after varying lengths of time. In the resistant state, cells were at least as sensitive as their parental populations to the antiviral effects of IFN when vesicular stomatitis virus was used as the challenge virus, suggesting that resistance to the antiproliferative effects of IFN does not necessarily correlate with changes in sensitivity to its antiviral effects. The sensitivities of the IFNr lines to the antiproliferative effects of the synthetic dsRNA, rInrCn, were characterized. Resistant lines of both HT1080-2 and RT4-1 clones displayed the same sensitivity to rInrCn-mediated toxicity as did their respective parental HT1080-2 and RT4-1 lines. Luria-Delbruck analysis indicated that the INFr trait is a non-randomly acquired phenotype probably induced by IFN at the time of selection. The IFNr cells retain sensitivity to the antiviral effects of IFN, as well as to the antiproliferative effects of dsRNA. (24 Refs)

10. STUDIES ON ANTITUMOR ACTIVITY OF INTERFERON 1. EFFECT OF INTERFERON ON HUMAN HEMATOPOIETIC CELL LINES GROWN IN VITRO.

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Okayama Igakkai Zasshi; 93(7/8):739-748 1981

A total of 12 hematopoietic cell lines was tested for in vitro sensitivity to interferon (IF). The cell lines were four T-cell ALL lines (TALL-1, MOLT-4, HPB-ALL, HSB-2), one ATL line (MT-1), two null-cell ALL lines (NALL-1, KOPN-8), one pre-B-cell ALL line (NALM-18), one B-cell line (BALL-1), one myeloma line (Oda), one Burkitt lymphoma line (JBL-3) and one APL line (HL-60). At a concentration of 1,000 U/ml, all four T-cell ALL lines, NALM-18, NALL-1 and Oda showed high or moderate sensitivity to the growth inhibition effect of IF. BALL-1 showed slight sensitivity and its in vitro growth was considerably inhibited at a higher concentration of IF (5,000 U/ml). However, MT-1, JBL-3, KOPN-8 and HL-60 were resistant to IF and their in vitro growth was not inhibited at all even at the concentration of 1,000 U/ml. MT-1 cells, although resistant to IF in suspension culture, were sensitive in agar culture. Colony formation was markedly inhibited at a concentration of 1,000 U/ml. The mechanism of growth inhibition by IF and the implications of the present findings are discussed. (Author abstract) (40 Refs) (In JPN)

11. INTERFERON PRODUCTION AND NATURAL KILLER CELL ACTIVITY OF PERIPHERAL BLOOD LYMPHOCYTES FROM NORMAL CHILDREN AND ADULTS AND PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA (MEETING ABSTRACT)

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Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

The erythroleukemia cell line K562 has been shown to stimulate normal lymphocytes into interferon (IFN) production. Also natural killer (NK) cell activity correlated with amount of IFN produced. In our studies peripheral blood lymphocytes (PBL) from normal controls and children undergoing treatment for Acute Lymphoblastic Leukemia (ALL) were tested simultaneously for NK activity and IFN production against K562. NK cell activity using Cr51 release was measured after 4 hour incubation of the microtiter plates at 37 C/5% CO2. IFN production required replenishment of the wells with culture medium and incubation at 37 C/5% CO2 for 18 to 24 hours. Supernatants were assayed for IFN a dye-uptake assay in Vero cells challenged with Semliki Forest virus. Seven of 9 PBL samples from normal adults produced IFN (range 19-43 units/ml) and simultaneously gave NK cell activities of 13-54% (mean 31%). Similarly 4/5 samples from normal children (age range 11 months to 11 years) produced IFN (range 16-43 units/ml) and gave a range of NK cell activities 6-20% (mean 13%). Conversely 12 child ALL patients (less than 1% blasts in PBL) were negative for IFN production and gave low values for NK cell activity (range 0-17%; mean 6%). Medium alone samples were negative. Previous studies showed that ALL patients were immunosuppressed in absolute numbers of T and B lymphocytes. Our results have further shown that immunosuppressive treatment also impairs lymphocyte function in these patients. (2 Refs)

12. ANALYSIS BY A SINGLE CELL CYTOTOXICITY ASSAY OF NATURAL KILLER (NK) CELL FREQUENCIES AMONG HUMAN LARGE GRANULAR LYMPHOCYTES AND OF THE EFFECTS OF INTERFERON ON THEIR ACTIVITY.

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J Immunol; 128(6):2514-2521 1982

We have determined binding and lytic capacities of human peripheral blood lymphocytes (PBL) and of highly purified large granular lymphocytes (LGL) against various anchorage-dependent and suspension-grown target cells by using a single cell cytotoxicity assay in agarose. The effects of interferon (IFN) on these effector cell functions were also studied. The kinetics of the recycling capacity of LGL after the initial conjugation with target cells was studied by inspecting purified conjugates that were formed in target cell excess. After initial LGL-K563 interaction, the majority of conjugates dissociated spontaneously. Non-IFN-pretreated effector cells were refractory to rebinding for 2 hr, after which the binding capacity reappeared. IFN-pretreated LGL were continuously capable of rebinding after the initial dissociation, indicating that IFN increases the recycling capacity of NK cells. Thus, IFN can affect the recycling capacity of NK cells. Thus, IFN can affect NK activity in up to four different ways: (a) by converting some nonbinding LGL to target-binding LGL, (b) by activating nonlytic binding LGL, (c) by increasing the rate of lysis of lytically active binding NK cells, and (d) by facilitating recycling of NK cells by eliminating refractoriness to rebinding by LGL. When LGL were tested for binding capacity toward a mixture of seven different target cells, an increased binding frequency was detected, as compared with the frequency of binding to any one of the target cell lines. This result suggests some selectivity in the binding of NK cells to target cells. Based on sequential conjugations of LGL with a single target cell and the observed selectivity in binding, we estimate that up to 80% of LGL can function as NK cells. This close association of LGL and NK activity indicates the value of morphologic analyses of effector cell populations in the assessment of human NK activity. (Author abstract) (26 Refs)

13. STIMULATION OF NATURAL CYTOTOXIC ACTIVITY IN MIXED CELL CULTURES AND BY CULTURE SUPERNATANTS CONTAINING INTERFERON.

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Immunology; 46(2):401-409 1982

We have previously demonstrated that lymphocyte preparations cultured for 5 days with a number of different mitomycin-C-treated lymphoid cell lines showed increased non-specific (NK-like) cytotoxic activity. We have now examined the activity induced in T- and B-cell-enriched responder populations, prepared by sheep red blood cell (SRBC) rosette separation, and found that increased cytotoxic activity was present mainly in the T-cell-enriched fraction. To investigate whether soluble factors were involved in the mediation of enhanced cytotoxicity, freshly isolated effector cell populations before measurement of cytotoxicity against K562 cells. Effector cells pretreated with supernatants from mixed cell cultures incubated for 2-6 days showed increased cytotoxic activity, the greatest activity being obtained with supernatants from 4 and 5 days co-cultures. Increased activity was observed when effector cells were pretreated for 2, 4 and 18 hr with supernatants from mixed cell cultures, regardless of the nature of the stimulator cell (T- and B-cell derived lines, K562 and normal allogeneic lymphocytes). Active supernatants were produced by T-cell-enriched, but not B-cell-enriched responder populations. Supernatants from mixed cell cultures were also examined for the presence of interferon (IFN) and in general, those mediating large increases in cytotoxic activity also contained significant anti-viral activity. The IFN detected was not neutralized by antiserum to IFN-beta but was partly neutralized by antiserum to IFN-alpha. pH 2 treatment also removed part of the activity while a combination of pH 2 and anti-alpha completely neutralized the activity suggesting the presence of IFN-gamma and IFN-alpha. The candidacy of IFNs as mediators of enhanced cytotoxicity in this system is discussed. (Author abstract) (39 Refs)

14. INTERFERON INHIBITS PWM INDUCED B CELL DIFFERENTIATION BUT NOT ONSET OF PROLIFERATION.

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Leuk Res; 6(2):221-229 1982

Results of a test, using pokeweed mitogen (PWM) driven human lymphocyte system to elicit an in vitro humoral response are reported. The net DNA synthesis by PWM stimulated cells was reduced by approx 40% in the presence of interferon (INF) after 96 and 144 hr of culture. The presence of INF resulted in reduced net synthesis of DNA, indicating reduced net cell proliferation due to INF. The distribution of cells with respect to the G1/0-, S-, and G2 + M-cell cycle phases was similar in PWM stimulated cell cultures with or without INF. INF treated cells initiated DNA synthesis at the same time as untreated cells. The presence of INF, thus, did not affect the minimum transit from G0 to S. No difference in the population size was observed for cells in the presence or absence of INF until after 48 hr. However, the size of INF treated populations thereafter was persistently less. This is consistent with the INF induced reduced proliferation. The smaller population size of INF exposed populations is attributable to the reduction in proliferation rate relative to the loss rate. The rates of PWM induced proliferation by T cells and non-T cells were approx equal and reduced similarly in the presence of INF. The observed fraction of the population composed of T cells remained stable up to 144 hr for both cells treated and not treated with INF. The enrichment in the relative number of plasmacyte producing either kappa or lambda light chain antibody, due to PWM induced B cell differentiation, was reduced by INF. The observed reduced protein synthesis rate corroborates the reduced enrichment of immunoglobulin producing cells due to INF. (28 Refs)

15. MECHANISM OF STIMULATION BY HUMAN INTERFERON OF PROSTAGLANDIN SYNTHESIS IN HUMAN CELL LINES.

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Cancer Res; 42(8):3209-3214 1982

Human interferon beta (IFN-beta) stimulated the synthesis of prostaglandin E (PGE) and prostaglandin F2alpha in IFN-sensitive RSa and GM258 cell lines, but not in IFN-resistant HEC-1 cells. IFN-beta at a concentration of 1,000 units/ml elicited two- to three-fold increases in PGE production in these cell lines. In the presence of exogenous arachidonic acid (1 ug/ml), IFN-pretreated cells produced five-fold more PGE compared to the cell cultures in the absence of arachidonic acid. Prednisolone, an inhibitor of phospholipase A2, at a concentration of 2 ug/ml inhibited the enhanced synthesis of PGE by IFN-pretreated cells. Indomethacin (4 ug/ml), a potent fatty acid cyclooxygenase inhibitor, also inhibited the increased synthesis of PGE. IFN stimulated the release of [14C]arachidonic acid from phospholipids but did not stimulate the activity of fatty acid cyclooxygenase. These data suggest that IFN stimulates prostaglandin synthesis by promoting the release of arachidonic acid from phospholipids. Since cycloheximide and actinomycin D inhibited the stimulation of PGE synthesis, the stimulation of prostaglandin synthesis by IFN seemed to be due to de novo enzyme synthesis, which catalyzes the release of fatty acid. Addition of exogenous PGE suppressed the growth of RSa and GM258 cells. Prednisolone and iodomethacin partially inhibited anti-cell growth activity of IFN, suggesting a possibility that IFN-inhibited cell growth was partly mediated by prostaglandins. (Author abstract) (55 Refs)

16. IMMUNE (Y) INTERFERON PRODUCTION BY MURINE T CELL LYMPHOMAS.

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J Immunol; 128(6):2807-2809 1982

Various cloned murine T cell hybridomas and T cell lymphomas were evaluated for their ability to produce interferon (IFN). Two T cell tumor clones, L12-R1 and L12-R4, derived from the spontaneously in vitro transformed cell line L12 originally established from fetal calf serum-primed C57BL/6 spleen cells were found to produce high IFN amounts upon mitogen stimulation. Phorbol myristate acetate led to maximal IFN production (2,187 IU) by L12-R4 cells at concentrations of 2 x 10(-7) M, whereas concanavalin A and phytohemagglutinin induced lower levels of IFN synthesis (160 to 243 IU). None of the cell lines tested produced IFN constitutively or upon lipopolysaccharide stimulation. The IFN was characterized as immune (y) by being labile at pH 2 and neutralized by two rabbit anti-murine IFN-y antisera but not by antiserum to murine leukocyte (alpha) and fibroblast (beta) IFN. Phenotypic characterization of IFN-y-producing cells showed the L12 clones to be Thy-1.2+, Lyt-1+, 23-, and Ig-. The L12-R4 tumor cells therefore provide a unique source of IFN-y for purification, and may represent a useful model for studying the molecular mechanisms involved in T cell differentiation leading to IFN-y production. (Author abstract) (24 Refs)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

17. ON THE POSSIBILITY OF IMMUNOTHERAPY FOR OSTEOGENIC SARCOMA OF THE BONE USING ANAEROBIC CORYNEBACTERIUM PARVUM.

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Dept. Orthopedics, Yokohama City Univ., Yokohama, Kanagawa, Japan
Nippon Seikeigeka Gakkai Zasshi; 55(9):844-846 1981

When Corynebacterium parvum, at an optimum dose of 0.5 mg, was given to mice carrying transplanted methylcholanthrene-induced sarcoma, the growth of the tumor was markedly inhibited. Histologically, necrosis of tumor cells was seen 2 wk after treatment with C parvum. The av survival period was 19 days, whereas the group given 2.5 mg/kg of adriamycin (ADR) survived for 35 days. The survival period was 45 days for the group given a combination of ADR (0.5 mg/kg) and C parvum. When C parvum was given to the mice carrying transplanted Lewis tumor (which has a high rate of metastasis to the lung), the number of mice with lung metastasis was reduced to only a few compared to 100% lung metastasis in control mice. C parvum also decreased the tumor incidence induced by 3-methylcholanthrene to only two ICR mice. Similar experiments with nude mice (nu/nu) and nu/+ mice showed that T cells are probably required for tumor controlling effect of C parvum injection. Clinically, C parvum was given 4 mg/wk for 5 wk. Among 14 osteosarcoma patients that were treated with C parvum in 6 yr, 5 were alive for more than 4 yr. The observation time for the other nine patients two of whom died, is to short for any conclusions. Other therapies, such as chemotherapy, radiotherapy and surgery were used whenever possible. Therefore, the improved prognosis may have been due to these therapies. C parvum treatment may have played some roles in controlling tumor growth and metastasis to the lung. (no Refs) (In JPN)

18. ANTI-TUMOR CYTOSTATIC AND CYTOTOXIC PROPERTIES OF PERITONEAL CELLS OF CONVENTIONAL AND GERM-FREE MICE, STIMULATED OR NOT WITH 'CORYNEBACTERIUM PARVUM'.

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Ann Immunol (Paris); 133C(1):33-43 1982

Conventional mice (BALB/C males) treated with Corynebacterium parvum showed significant increases in the number of peritoneal cells. When germ-free mice (BALB/C males and females) were injected with C parvum, there was no significant modification in the number of peritoneal cells. The percentage of adherent cells increased significantly (p greater than 0.02) in conventional mice but remained constant in the germ-free mice. After treatment with C parvum, all the conventional and germ-free mice presented equivalent cytostatic properties against YC8 tumoral target cells. In conventional mice, nonactivated cells had a significant cytostatic effect (42%) on K BALB fibroblasts only when the ratio of effector cells to target cells was 40. The treatment of mice with C parvum significantly increased the cytostatic effects (97%) of effector cells. In germ-free mice, the cytostatic properties were from 51% to 84% with significantly higher cytostasis following activation with C parvum. In conventional mice, cytotoxic properties increased following activation with C parvum but in germ-free mice, cytotoxic properties were unchanged. It is suggested that variable microbial flora in conventional mice could cause variable cytotoxic and cytostatic reactions following treatment with C parvum. (24 Refs) (In FRE)

19. CORYNEBACTERIUM PARVUM PREVENTS IMMUNIZATION TO ADMIXED IRRADIATED TUMOR CELLS BY A LOCAL PROCESS.

Titus MJ, Bartlett GL, Kreider JW
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Int J Cancer; 29(6):699-705 1982

Immunization of mice with 10(6) irradiated LSTRA murine leukemia cells (LX) induced weak immunity to subsequent tumor-cell challenge. Admixture of low doses (1.4-14 ug) of C parvum with the LX usually augmented the immunity. Higher doses (1,400-7,000 ug) of admixed C parvum not only failed to augment immunity, but prevented immunization by the contained LX. We investigated the mechanism by which 1,400 ug of C parvum mixed with 10(6) LX prevents immunization by the LX. The inhibitory effect was a function of the ratio of C parvum to tumor cells. Injection of 1,400 ug C parvum, alone or mixed with the LX, did not prevent immunization by LX given simultaneously at a separate site. Injection of C parvum, alone or mixed with the LX, did not prevent immunization by LX injected simultaneously at a separate site sharing a common lymph-node drainage area. The high dose of C parvum prolonged retention of radiolabeled LX at the injection site and decreased the rate of distribution of the LX to other organs, particularly the spleen. These results indicate that a high dose of C parvum prevented immunization through a localized process at the injection site. (Author abstract) (19 Refs)

20. IN VITRO AND IN VIVO CYTOTOXICITY INDUCED BY AN ATTENUATED SALMONELLA: RELATION TO BACTERIAL CARRIER STATE AND RESISTANCE TO TUMOUR GROWTH.

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Aust J Exp Biol Med Sci; 60(1):1-21 1982

In vivo and in vitro parameters of tumor resistance were examined after immunization of mice with the attenuated 11RX strain of S enteritidis. During the bacterial carrier state produced by intraperitoneal (ip) or intravenous (iv) injection of 11RX the mice were resistant to ip tumor growth, could destroy ip injected 125I- or 131I-labeled tumor cells in vivo and had non-specifically cytotoxic peritoneal cells (PC) which could lyse 51Cr-labeled tumor cells in vitro. Most of the in vivo and in vitro cytotoxic activity could be attributed to activated macrophages. The predominantly local nature of 11RX-induced anti-tumor activity was indicated by the superiority of the ip route of infection for induction of tumor resistance and in vivo and in vitro cytotoxicity. After iv injection of 11RX, none of the anti-tumor effects outlasted the bacterial carrier state. However, after ip infection, a dichotomy was observed between in vitro and in vivo anti-tumor effects. In vitro PC cytotoxicity lasted only for the length of the 11RX carrier state (approx 30 days), whereas resistance to ip tumor growth lasted for 60 to 100 days and was correlated closely with cytotoxic activity measured in vivo. Possible reasons for this dichotomy are discussed. (Author abstract) (36 Refs)

CYTOKINE THERAPY

21. MECHANISMS OF TCGF PRODUCTION BY CLONED T-CELL LINES: CHARACTERIZATION OF PRODUCER LYMPHOMA LINES AND KINETICS OF PRODUCTION.

Smith RT, Shimizu S, Norcross MA, Maino VC

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Clin Immunol Immunopathol; 23(2):286-296 1982

The activation requirements and kinetics of production of T-cell growth factor are described for a stable, cloned T-lymphoma line, EL4-G-12. The line yields a product which has the biochemical and biological attributes of TCGF of normal cell origin examined thus far. Production is dependent upon a transmembrane signal which can be provided by known T-cell-activating lectins, and by antibody to a specific ligand on the Thy-1 molecule, if accessory cells or factors are provided. Production is rapid, beginning within 4 hr, and ceasing between 12 and 18 hr depending upon cell density, signal intensity, and culture conditions. DNA synthesis ceases as production begins, and release is not a result of cell death. It has not yet been determined whether rapid synthesis de novo, or activation and release of an inactive hormone precursor explains the production kinetics observed. (Author abstract) (17 Refs)

22. DISTINCT SIGNALS FOR ANTIBODY-DEPENDENT AND NONSPECIFIC KILLING OF TUMOR TARGETS MEDIATED BY MACROPHAGES.

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J Immunol; 129(1):427-432 1982

Conditions influencing the generation of antibody-dependent cellular cytotoxicity (ADCC) and several types of nonspecific tumor cell killing by macrophages were compared. Resident mouse peritoneal macrophages and several macrophage cell lines spontaneously display very low levels of ADCC to lymphoma targets. However, ADCC could be greatly stimulated in these macrophage populations by several days of culture with lipopolysaccharide (LPS), tumor promoter phorbol myristic acetate (PMA), and lymphokine (LK) preparations. Fibroblast L cell-conditioned medium (L-CM), a source of activities required for in vitro macrophage colony formation, also augmented ADCC. Two days of preincubation was optimal for stimulation of this cytotoxic activity. In contrast to these results, pretreatment of macrophages with any of the agents inhibitor tumor toxicity induced by nonspecific activating drugs present during the assay. This inverse relation between ADCC and nonspecific killing after pretreatment was obtained with peritoneal cells and two cloned macrophage cell lines. Thus, although the same cell or cell type can mediate both types of killing, the two mechanisms seem to be mediated by distinct states of a macrophage. The ADCC-stimulating agents, LPS, LK, and L-CM, probably have a common pathway of activation, because dexamethasone at 10(-6) M inhibited their effect. The factors in the LK and L-CM that stimulate ADCC are distinct from LPS, because the endogenous activities were inactivated by boiling. The activities are also separate from interleukin 2 and myeloid colony-stimulating factor purified from L-CM, CSF-1, had no effect on macrophage tumoricidal activity. ADCC-stimulating activity was not the same as macrophage-activating factor for nonspecific killing of fibrosarcoma targets, because the latter is not found in L-CM. It is concluded that macrophage ADCC and nonspecific cytotoxicity may be regulated by different endogenous signal and may represent different states of stimulated macrophages. (Author abstract) (41 Refs)

23. LYMPHOKINE-ACTIVATED KILLER CELL PHENOMENON. LYSIS OF NATURAL KILLER-RESISTANT FRESH SOLID TUMOR CELLS BY INTERLEUKIN-2-ACTIVATED AUTOLOGOUS HUMAN PERIPHERAL BLOOD LYMPHOCYTES.

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J Exp Med; 155(6):1823-1841 1982

It had previously been reported that peripheral blood leukocytes from cancer patients could be activated in culture by preparations of interleukin-2 (IL-2), resulting in the development of effector cells cytotoxic for autologous fresh solid tumors in short-term 51chromium release assays in greater than 90% of cancer patients tested. A study is presented which further characterizes the IL-2-induced antitumor cytotoxicity phenomenon. Major features of the lymphokine-activated killer (LAK) system include: (1) LAK lysing of natural killer (NK)-resistant fresh solid tumor cells; (2) LAK could be generated by a 2-3 day culture in IL-2 containing supernatants, from either allogeneic or autologous sources; (3) immune interferon was not the primary stimulus responsible for LAK; (4) neither precursors nor LAK effectors were adherent cells; (5) LAK precursors were found in NK-void thoracic duct lymphocyte populations, as well as in peripheral blood lymphocytes (PBL) of normal subjects and PBL of cancer patients; (6) LAK development was radiation sensitive; and (7) LAK effectors expressed the serologically defined phenotype of T cells. These findings suggested that the human LAK phenomenon is distinct from the NK and cytotoxic T lymphocyte systems. (44 Refs)

24. CONSTITUTIVE INTERLEUKIN 2 PRODUCTION BY THE JURKAT HUMAN LEUKEMIC T CELL LINE.

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Eur J Immunol; 12(5):387-392 1982

Interleukin 2 (OL2) is a lymphokine produced from phytohemagglutinin (PHA)-stimulated peripheral blood mononuclear cells and characterized biologically by its ability to maintain the in vitro proliferation of activated T cells. In a search for a convenient alternative source of biologically active human IL2, cells from the five established T cells lines, MOLT4, HSB2, CCRF-CEM, RPMI 1301 and JURKAT were cultured at high concentrations for 18-36 h (induction cultures), and their cell-free supernatants thereafter screened on IL2-dependent cultured human and mouse T cells. MOLT4, HSB2, RPMI 1301, and CCRF-CEM all failed to produce detectable levels of IL2. Of the three JURKAT cell lines obtained from different sources, one, designated JMN, produced high levels of IL2 activity. A second, JM, failed to produce any IL2, while the third, JHAN, produced intermediate levels. Stimulation of the LL2-producing JMN or JHAN variants with PHA, the phorbol diester 12-0-tetradecanoyl-phorbol-13-acetate (TPA), or both PHA and TPA together, resulted in an apparent increase of IL2 activity in the culture supernatant when assayed by a short-term tritiated thymidine incorporation test. However, both PHA and TPA added directly to the test cells caused substantial thymidine incorporation. Moreover, the nonproducer line JURKAT-JM could not be converted to an IL2 producer by stimulation with PHA, TPA, or both. When JMN supernatants were used to support actual long-term growth and cloning of T cells in limiting dilution, the constitutively produced IL2 was superior to that produced after PHA and/or TPA stimulation. Addition of TPA, but not of PHA, to lectin and TPA-free JMN IL2 resulted in a decreased ability of such supernatants to support clonal T cell growth, suggesting that TPA had a growth-inhibiting effect. These results show that the continuously growing JURKAT-JMN cell line could provide a suitable source of mitogen-free human IL2. (Author abstract) (25 Refs)

ACTIVE SPECIFIC IMMUNIZATION

25. ERADICATION BY ACTIVE SPECIFIC IMMUNOTHERAPY OF ESTABLISHED TUMOR TRANSPLANTS AND MICROSCOPIC LYMPH NODE METASTASES.

Yarkoni E, Ashley MP, Zbar B, Sugimoto T, Rapp HJ
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Cancer Res; 42(7):2544-2546 1982

Guinea pigs, each with an established syngeneic dermal line 10 tumor and microscopic lymph node metastases, were immunized by injection of a mixture of irradiated line 10 tumor cells and an oil-in-water emulsion containing heat-killed cells of Mycobacterium bovis strain Bacillus Calmette-Guerin. Squalene or squalene-in-water emulsions, prepared by ultrasonication and containing mg doses of mycobacterial cells, were effective adjuvants. Immunization eradicated established dermal tumors (about 10 mm in diameter) and prevented growth of microscopic lymph node metastases. Untreated animals (animals treated by intradermal administration of Bacillus Calmette-Guerin cells attached to oil droplets alone or with irradiated tumor cells alone) all died with progressive tumor growth. (Author abstract) (16 Refs)

26. AUTOLOGOUS LYMPHOCYTOTOXICITY AGAINST SQUAMOUS CELL CARCINOMA IN HEAD AND NECK: II. EVIDENCE OF AUTOLOGOUS LYMPHOCYTOTOXICITY AGAINST TUMOR CELL.

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Nippon Jibiinkoka Gakkai Kaiho; 84(12):1579-1587 1981

The established cell line, KOIMC-011 (at 18 24 passages) derived from human squamous cell carcinoma, was treated with mitomycin C (MMC) to be used as a cell stimulator. When such MMC-treated KOIMC-011 cells were mixed and incubated with autologous lymphocytes, derived from the host of KOIMC-011, at lymphocyte/tumor cell ratio of 10:1, lymphocytotoxicity was significantly induced (20.8% 51Cr release) compared to the lymphocytes incubated alone (9.1% 51Cr release). The cytotoxicity was in the T cell fraction and not in the non-T cell fraction, and was blocked by monoclonal anti-human less-2A antibodies. Non-target K562 cells heat treated, rabbit anti-IgG treatment, and phytohemagglutinin treatment did not block the T cell cytotoxicity. When stimulated T lymphocytes were treated with anti-HLA sera, only anti-HLA against CW3 reduced the T cell cytotoxicity. The ability to induce cytotoxicity was not affected by freeze and thawing of the tumor cells. These results suggest the possibilities of the involvement of autologous HLA antigen in the destruction of tumor cells, and of specific immunotherapy against human cancers. (32 Refs) (In JPN)

SEROTHERAPY AND RELATED APPROACHES

27. PLASMA PERFUSION OVER IMMOBILIZED PROTEIN A FROM STAPHYLOCOCCUS AUREUS FOR TREATMENT OF CANCER: OBSERVATIONS ON THE EVOLUTION OF PLASMA PERFUSION SYSTEMS.

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Int J Artif Organs; 5(2):77-80 1982

The development of plasma perfusion systems capable of inducing tumor necrolytic responses in cancer patients is described. Comprehensive morphologic and immunologic descriptions of a rapid and extensive tumor killing response in 12 dogs with mammary adenocarcinoma after a single extracorporeal perfusion over immobilized heat inactivated and formalin fixed Staphylococcus aureus Cowans 1 (SpA) which was not seen after perfusion over protein A deficient Staphylococcus were reported previously. Three of these dogs died within 24 hr after perfusion. Subsequently, purified protein A was immobilized in a colloidion charcoal matrix and placed in a column on the plasma line of plasma-cell separator. A total of 13 procedures in 8 dogs was carried out with this system followed by chemotherapy after five treatments. Acute tumor killing responses were observed after these procedures which were enhanced when cytosine arabinoside was given after perfusion. In the treatment of five patients with breast adenocarcinoma, this system of perfusion was used off-line, followed by direct infusion into the patients. Patients experienced acute tumor pain, morphologic changes in tumor, and tumor regression. The potential of this system in multi-modality cancer treatment, and some complications observed in the limited patient population studied to date, are discussed. (10 Refs)

28. A MONOCLONAL ANTIBODY (MMA) THAT IDENTIFIES A DIFFERENTIATION ANTIGEN ON HUMAN MYELOMONOCYTIC CELLS.

Hanjan SN, Kearney JF, Cooper MD
Kailestad Lab., Inc., P.O. Box 18029, Austin, TX, 78760
Clin Immunol Immunopathol; 23(2):172-188 1982

A monoclonal IgMkappa antibody (MMA) was produced against the human histocytic cell line, U-937. This antibody reacted by indirect immunofluorescence and complement-mediated lysis with adherent mononuclear cells and granulocytes. MMA was unreactive with circulating T and B cells, erythrocytes, and platelets. Depletion of MMA+ cells from blood mononuclear cell populations significantly reduced the reactivity of these cells to antigens and mitogens. The lymphoproliferative responses were restored by addition of 10% MMA+ cells. MMA is expressed by some T-cell lines (HSB-2, MOLT-3, MOLT-4) and mitogen-activated T cells, but not by B-cell lines or activated B cells. Studies using double immunofluorescence showed that 80% of activated T4+ and 10% of T8+ cells expressed MMA. The antigen is present on precursors of in vitro granulopoietic colony-forming cells. Malignant cells from patients with both acute and chronic myeloid leukemias express this antigen. The MMA antibody thus defines a unique differentiation antigen present on human myeloid cells, their precursors, and a subpopulation of activated T cells. (Author abstract) (45 Refs)

29. MONOCLONAL ANTIBODIES TO HUMAN PROSTATE AND BLADDER TUMOR-ASSOCIATED ANTIGENS.

Starling JJ, Sieg SM, Beckett ML, Schellhammer PF, Ladaga LE, Wright GL
Dept. Biochemistry, Eastern Virginia Medical Sch., Norfolk, VA, 23501
Cancer Res; 42(8):3084-3089 1982

Monoclonal antibodies to human prostate adenocarcinoma membrane antigens were produced by fusion of P3X63/Ag8 mouse myeloma cells with spleen cells from BALB/c mice immunized against the prostate cancer cell line DU145. The hybrids were screened for antibody production using glutaraldehyde-fixed cells in a solid-phase radioimmunoassay. Antibody-binding specificity was also checked by quantitative adsorption, membrane immunofluorescence, and complement-dependent cytotoxicity assays. A hybridoma clone (83.21) was isolated that secreted antibodies which preferentially bound to several prostate and bladder cancer cell lines but did not bind to a variety of other normal and malignant human cell lines. This antibody also reacted with a cytomegalovirus-transformed human embryonic lung cell line but not to normal human embryonic lung cells. Quantitative adsorption studies demonstrated that the 83.21 monoclonal antibody was strongly reactive to membrane preparations from human prostate adenocarcinoma tissue and a liver metastasis of prostate carcinoma. Little or no binding activity was observed against two other prostate carcinomas, benign prostatic hyperplasia, normal prostate, or normal liver. Binding studies indicate that the 83.21 monoclonal antibody does not bind to alpha-fetoprotein, carcinoembryonic antigen, prostatic acid phosphatase, human leukocyte antigen, Beta2-microglobulin, HLA-Dr antigens, fibronectin, or prostate antigen. The data indicate that we have isolated a monoclonal antibody that binds to an antigen(s) expressed by several urogenital carcinoma cell lines as well as human prostate tumor tissue and that the antibody is not directed against well-known human tumor cell markers. (Author abstract) (37 Refs)

30. MOUSE MONOCLONAL ANTIBODY TO A MELANOMA-CARCINOMA-ASSOCIATED ANTIGEN SYNTHESIZED BY A HUMAN MELANOMA CELL LINE PROPAGATED IN SERUM-FREE MEDIUM.

Chee DO, Yonemoto RH, Leong SP, Richards GF, Smith VR, Klotz JL, Goto RM, Gascon RL, Drushella MM
Oncology Lab., Inc., Fiskeville, RI, 02823
Cancer Res; 42(8):3142-3147 1982

A monoclonal antibody, F11, was produced against a tumor-associated antigen from the spent medium of the M14 human malignant melanoma cell line which was grown continuously in serum-free medium. Ouchterlony double-diffusion study revealed that the F11 monoclonal antibody is an immunoglobulin G1. The F11 monoclonal antibody reacted positively with seven of eight (88%) melanoma, five of five (100%) carcinoma, zero of five normal, and zero of two lymphoblastoid cell lines by indirect immunofluorescence test. Also, by indirect immunofluorescence test, F11 monoclonal antibody reacted with cryostat sections from four of five (80%) melanomas, six of seven (86%) carcinomas, zero of one benign nevus, and zero of two benign breast diseases. By the indirect avidin:biotin:peroxidase complex immunoperoxidase method, the F11 monoclonal antibody reacted positively with cryostat sections from five of five (100%) melanomas, five of five (100%) breast cancers, two of two (100%) colon cancers, zero of one benign nevus, and zero of one Hodgkin's disease spleen. Thus, the tumor-associated antigen that the F11 monoclonal antibody recognizes appears to be expressed by melanomas and carcinomas, hence the designation melanoma-carcinoma-associated antigen. Microscopic observations disclosed that the melanoma-carcinoma-associated antigen is present in the cytoplasm, on the membrane of melanoma and carcinoma cells, and in the lumen of glandular structures of breast and colon carcinomas. The mol wt of the melanoma-carcinoma-associated antigen in spent medium from the M14 CEM cell line is 100,000 as determined by sodium dodecyl sulfate: polyacrylamide gel electrophoretic analysis of indirect immunoprecipitates obtained with the F11 monoclonal antibody. (Author abstract) (37 Refs)

31. IMMUNOPEROXIDASE STAINING OF CARCINOEMBRYONIC ANTIGEN WITH MONOCLONAL ANTIBODIES IN ADENOCARCINOMA OF THE COLON.

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Histochemistry; 74(2):223-227 1982

Application of monoclonal antibodies to the immunoperoxidase staining of carcinoembryonic antigen (CEA) is described. A distinct positive staining of the neoplastic epithelial cells was seen in all sections stained with unadsorbed anti-CEA ascites fluids and the rabbit anti-CEA-antiserum. All controls including the ascites fluids adsorbed with purified CEA were negative. The nonspecific background staining of the ascites fluids was negligible in all dilutions used giving a better distinction than the rabbit antiserum. (9 Refs)

32. A MONOCLONAL ANTIBODY RECOGNIZING A HUMAN THYMUS LEUKEMIA-LIKE ANTIGEN ASSOCIATED WITH B2 MICROGLOBULIN (MEETING ABSTRACT).

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Imperial Cancer Research Fund, London, England

Eighth Annual Meeting of the American Association for Clinical Histocompatibility Testing, April 25-29, 1982, San Francisco, California. American Association for Clinical Histocompatibility Testing 41 pp., 1982.

A monoclonal antibody, M241, was produced which binds to a human cell surface molecule with properties similar to the murine thymus leukemia (TL) antigen. This human TL-like antigen was found on thymocytes and some T cell lines derived from patients with acute lymphocytic leukemia, but was not found on peripheral blood lymphocytes or B cell lines. The monoclonal antibody M241 was used to immunoprecipitate a molecule from lysates of 125I surface labeled MOLT 4 cells which had two subunits, a 43,000 molecular weight chain and a 12,000 molecular weight chain. The small subunit was shown to be Beta2-microglobulin (beta2-m) by immunoprecipitation with a monoclonal antibody, BBM.1, which recognizes human beta2-m. The TL-like molecule recognized by M241 was shown to be serologically distinct from the HLA-A,B,C molecules recognized by three antibodies W6/32, PA2.6 and BB7.8, and distinct from another human thymocyte antigen, the 49,000 molecular weight HTA 1 molecule, recognized by the monoclonal antibody NA1/34. Following removal of thr HLA-A,B,C molecules, the HTA 1 molecules, and the M241 defined TL-like molecules from MOLT 4 lysates, additional beta2-m associated molecules were immunoprecipitated with BBM.1. These molecules contained a 45,000 molecular weight subunit attached to beta2-m. (no Refs)

33. A NEW ACUTE LEUKEMIA-ASSOCIATED BLAST CELL ANTIGEN DETECTED BY A MONOCLONAL ANTIBODY.

Billing R, Lucero K, Shi BJ, Terasaki PI

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Blood; 59(6):1203-1206 1982

A monoclonal mouse antibody has been raised to the common acute lymphoblastic leukemia (cALL) cell line Reh. It is a cytotoxic antibody of the IgG2a subclass that reacts with leukemia cells from the following patients: 69% non-B non-T ALL, 50% T-ALL, 18% acute myeloblastic leukemia (AML), and 66% chronic myeloid leukemia (CML) blast crisis lymphoid cells. Other types of leukemia and all normal blood cells tested were negative, including T and B lymphocytes, granulocytes, monocytes, erythrocytes, and spleen cells. The detected antigen appears to be a type of blast cell antigen because it is also present on phytohemagglutinin (PHA) blast cells, myeloblast from normal bone marrow cells (by CFU-C), and all lymphoblastoid cell lines tested. Only one active antibody species could be detected by preparative isoelectric focusing on polyacrylamide gels and by protein-A-Sepharose affinity chromatography. (Author abstract) (17 Refs)

34. UTILITY OF MONOCLONAL ANTIBODIES IN THE IMMUNOLOGIC PHENOTYPING OF ACUTE LYMPHOBLASTIC LEUKEMIA.

Yu AL, Royston I, Leung KL, Kung FR, Hartman GA, Lightsey AL, Vangrove J, Sobol RE

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Hybridoma; 1(2):91-98 1982

Two monoclonal antibodies were used in conjunction with conventional lymphocyte markers to characterize acute lymphoblastic leukemia (ALL) in 34 children and 11 adults. Monoclonal antibody T101 detects a 65,000 mol wt cell surface antigen (T65) found on all T-cells in the peripheral blood and lymph node, T-cell lines, and thymocytes; the second antibody detects a monomorphic determinant on the Ia-like antigen, which is a bimolecular complex of 27,000 and 35,000 mol wt. Four distinct phenotypes were evident in the childhood ALL patients; the most common of these was observed in 22 patients. The marker profiles of the 11 adult patients exhibited the four phenotypes found in the childhood cases, and one additional phenotype. The most common phenotype, found in 6/11 patients, was the same as the most common phenotype in the childhood group. Reactivity with monoclonal anti-Ia and anti-T65 antibodies appears to define two distinct clinical subgroups of childhood ALL. The more common group was Ia+T65-and was characterized by an equal male:female distribution; younger age, lower leukocyte count, and lower incidence of organ involvement at presentation; and longer disease-free survival than Ia-T65+ patients. The less common Ia-T65+ group was associated with male predominance, anterior mediastinal mass, high leukocyte count, organ involvement, and early treatment failure. Anti-Ia and T101 reactivity are apparently mutually exclusive in ALL, since no Ia+T65+ patients were identified. (24 Refs)

35. A MONOCLONAL ANTIBODY WITH ANTI-BURKITT LYMPHOMA SPECIFICITY. I. ANALYSIS OF HUMAN HAEMATOPOIETIC AND LYMPHOID CELL LINES.

Wiels J, Lenoir GM, Fellous M, Lipinski M, Salomon JC, Tetaud C, Tursz T

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Int J Cancer; 29(6):653-658 1982

There is a hybridoma-produced monoclonal rat IgM (38-13) which appears to define a Burkitt's lymphoma-associated antigen (BLA). In this paper, we describe the reactivity of 38-13 with a panel of human hematopoietic and lymphoid cell lines. In indirect immunofluorescence (IF) assays, 15 of 26 Burkitt's lymphoma (BL) lines studied were clearly stained with 38-13 (from 13 to 100% positive cells) by microscope, with varying numbers of heavily labeled cells. In these positive cell lines, fluorescence-activated cell-sorter (FACS) analysis demonstrated that BLA was actually present on all the cells. Positive BL included Epstein-Barr virus (EBV) genome-carrying lines and EBV-negative ones; thus, BLA is not related to the presence of EBV. Most of the 15 BL cells that reacted with 38-13 contained a typical t(8;14) translocation, but had variant translocations such as t(2;8) and t(8;22). The cells were derived from BL patients of different geographical origins and clinical features. Four BL lines were poorly stained and seven were negative with 38-13 in IF assays. The 32 EBV-positive lymphoblastoid cell-lines (LCL) studied were negative. In three line pairs, consisting of a tumor line and an LCL from the same patient, only the BL line was demonstrated to react with 38-13. A series of non-BL cells, including hematopoietic, lymphoid and solid tumor lines, all failed to react with 38-13. Various attempts to modulate the expression of BLA on BL cells were unsuccessful. However, it cannot be ruled out that BLA is actually a transient B-cell differentiation marker. (Author abstract) (18 Refs)

36. MONOCLONAL ANTIBODIES REACTIVE WITH HUMAN MYELOID LEUKAEMIA CELLS.

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Clin Exp Immunol; 48(3):655-665 1982

Hybridomas producing monoclonal antibodies that bind to determinants on myelogenous leukemia blast cells were developed using fresh leukemia blasts as immunogens. These monoclonal antibodies were used to quantitate the amount of a variety of antigens on both leukemia and normal blood cells in a radioimmunoassay. The ability of these antibodies to mediate complement-dependent lysis of leukemia cells and normal blood cells was evaluated. Significant quantitative differences in the expression of a variety of cell surface antigens were observed among different myeloid leukemia cell samples, normal cells, and other forms of leukemia. However, none of the monoclonal antibodies studied were found to be specific for myeloblasts. Despite the fact that these antibodies bound to both leukemia and normal cells, several of them mediated complement-dependent cytotoxicity which was restricted to leukemic myeloblasts (AML-1-211, AML-2-30, CML-18, CML-75, CML-115, and CML-150). None of these clones, alone or in any combination, were capable of lysing normal lymphocytes or monocytes. Others were specifically cytotoxic to leukemia cell lines (AML-1-99). B cells and some leukemia samples (AML-2-9), and myelomonocytic leukemia cell samples and normal monocytes (AML-2-23). Several of the monoclonal antibodies from this panel appear to be promising for future clinical applications. (Author abstract) (32 Refs)

37. BIOLOGICAL ACTIVITY OF A MONOCLONAL ANTIBODY SPECIFIC FOR A RAT SARCOMA (MEETING ABSTRACT)

North SM, Dean CJ
Institute of Cancer Research, Clifton Avenue, Sutton, Surrey, SM2 5PX, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

A monoclonal antibody, (M10/76) of IgG2 isotype, directed against a tumor associated antigen of the chemically induced rat fibrosarcoma, MC24, is being used to investigate the role of humoral immunity in metastatic disease. To assess the biological activity of M10/76 in vivo, affinity purified antibody was injected iv into immunocompetent rats immediately before an iv challenge with viable tumor cells. After 16 days the animals were sacrificed and the number of lung colonies estimated. Lungs from the control groups had large numbers of tumor colonies, whereas lungs from animals treated with specific antibody contained no visible tumor colonies. Antibody M10/76 was also examined for its effects on spontaneous metastases in vivo. MC24 was grown in the hind limb of congenitally athymic male rats for 21 days and then removed by amputation of the hind limb. Specific antibody was administered iv at a dose of 50ug/rat given on alternate days throughout tumor growth and until 75 days post-amputation. The animals were then killed and examined for metastases. While all control animals showed metastases either to lung or lymph nodes, those treated with M10/76 showed either no metastatic lesions or enhanced metastatic disease. We conclude that Ab M10/76 is biologically active in vivo and is capable of influencing the course of metastatic disease. (no Refs)

38. THE EFFECT OF MONOCLONAL ANTIBODY-DIRECTED IMMUNOTOXINS AND IMMUNOMODULATORS ON CULTURED OSTEOGENIC SARCOMA CELLS (MEETING ABSTRACT)

Embleton MJ, Flannery GR, Pelham J, Rowland GF, Pihl A, Baldwin RW
Cancer Research Campaign Laboratories, University of Nottingham, Nottingham, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

A monoclonal antibody (MoAb) raised against an osteogenic sarcoma cell line, 791T, was conjugated to various cytotoxic drugs and toxins, and to Lymphoblastoid Interferon (IFN) mainly using N-succinimidyl-3-(2-pyridyldithio)-proprionate. Conjugates were tested for cytotoxic properties on 791T and several other cross-reactive osteogenic sarcoma cell lines using radioisotopic assays to measure protein or DNA synthesis. Virtually all immunotoxin conjugates retained antibody binding activity for 791T cells, in most, cytotoxic activity was lost or diminished compared with the unconjugated agent. The least inactivated were Vindisine/MoAb and Ricin A chain/MoAb, for which the LD50 values were approximately 100-fold and 30-fold less than the parent compounds respectively. IFN/Moab conjugates did not directly affect the cells, but IFN alone also had only a marginal cytostatic effect. However, IFN/MoAb was highly effective in stimulating natural killer (NK) cell activity against 791T and other target cells. 791T cells, but not antigenically unrelated cells, preincubated with the conjugate induced activation of NK cells against 51Cr-labelled third party cells in mixed culture. These studies indicate that further development is required for the preparation of immunotoxins, but suggest an alternative approach towards antitumor therapy using indirectly acting MoAb-directed immunomodulators. (no Refs)

39. SELECTIVE KILLING OF MALIGNANT CELLS IN A LEUKAEMIC RAT BONE MARROW USING AN ANTIBODY-RICIN CONJUGATE.

Thorpe PE, Mason DW, Brown AN, Simmonds SJ, Ross WC, Cumber AJ, Forrester JA
Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
Nature; 297(5867):594-596 1982

A model system in which lethally irradiated PVG rats were injected with a mixture of bone marrow cells and leukemic cells and in which the development of leukemia in the recipient rats was prevented by incubating the cells, prior to injection, with a monoclonal antibody W3/25-ricin conjugate that was selectively toxic to the leukemic cells is described. The W3/25 ricin conjugate was extremely effective in inhibiting protein synthesis by PVG leukemic cells. Leucine uptake was reduced by 50% on treatment of the cells for 1 hr at 37 C with the conjugate at a concentration of 1.4 nanog/ml ricin (2.2 x 10(-11) M). The percentage of cells which survived treatment with the conjugate in vitro was estimated by comparing the time that elapsed between the injection of the treated cells into PVG recipients and the appearance of leukemic cells in the peripheral blood with that observed when graded doses of untreated leukemic cells were injected. Rats which received 10(7) leukemic cells treated with the conjugate at 2.1 ug/ml ricin (10 ug/ml IgG) for 1 hr at 37 C in 100 milliM lactose and then washed twice in lactose-containing medium developed leukemia 8-10 days later than the recipients of untreated cells, indicating that the conjugate had destroyed approx 99.9% of the leukemic cells. Neither the treatment of cells in the presence of lactose with W3/25 antibody alone at 20 ug/ml nor treatment with antibody MRC OX8-ricin at 4.3 ug/ml ricin delayed the appearance of leukemia in the recipients. All recipients of untreated bone marrow/leukemic cell mixtures developed leukemia before their level of B-cell chimerism had been measured. None of the rats given W3/25-ricin-treated cell mixtures containing 10(3) leukemic cells developed disease and of three recipients of inocula containing 10(4) leukemic cells only developed disease. (14 Refs)

OTHER BIOLOGICAL RESPONSE MODIFIERS

40. INDUCTION OF ANTITUMOR IMMUNITY BY TUMOR CELLS TREATED WITH ABRIN.

Shionoya H, Arai H, Koyanagi N, Ohtake S, Kobayashi H, Kodama T, Kato H, Tung TC, Lin JY
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Cancer Res; 42(7):2872-2876 1982

Abrin is known as a cytotoxic lectin. Immunization with Meth-A tumor cells which were treated in vitro with abrin induced a strong antitumor immunity in syngeneic BALB/c mice. The immunizing effect was stronger than that produced by an irradiated Meth-A tumor cell vaccine. Studies on the mechanisms of the immunizing effect with the abrin-treated tumor cells demonstrated that abrin acts as an immunoadjuvant. Furthermore, the regression of a growing Meth-A tumor was observed after abrin was injected into the tumor, while the induction of a strong antitumor immunity also occurred. It appears, therefore, that the antitumor effects of abrin are attributable to two kinds of activity: cytotoxicity and adjuvant activity. (Author abstract) (27 Refs)

41. PROTEIN A ADSORPTION OF ACUTE MYELOGENOUS LEUKEMIA SERUM INDUCES IN VITRO BLAST LYSIS.

Miller WJ, Branda RF, Hurd DD, Wachsman W, Nelson NL, Jacob HS
Univ. Minnesota Hosp., Box 480, Mayo Building, 420 Delaware St. S.E., Minneapolis, MN, 55455
Blood; 59(6):1344-1347 1982

We studied cytotoxic activity of acute myelogenous leukemia (AML) sera for AML blasts before and after immunoadsorption with Staphylococcus aureus, Cowan I (SAC), which contains protein A. We found in vitro that incubation with treated AML sera reduced viability to 42.7% of control (p less than 0.01) for autologous and 21.0% of control (p less than 0.01) for allogeneic blasts. Normal peripheral blood cells were not killed by treated AML sera. Wood 46 strain of Staphylococcus aureus, which does not contain protein A, did not significantly reduce AML blast viability (94.8%, p greater than 0.4), while Sepharose-bound protein A reduced viability to 63.8% (p less than 0.01). Cytotoxicity does not appear to be complement-mediated, but cytotoxic activity is trypsin-sensitive and is contained in the immunoglobulin fraction. This model for study of the tumoricidal action of protein A adsorption should be useful for predicting utility of plasma adsorption as a therapeutic adjunct in the future. (Author abstract) (11 Refs)

CLINICAL IMMUNOLOGY

42. LEVELS OF CIRCULATING IMMUNE COMPLEXES IN PATIENTS WITH OVARIAN CANCER.

Clarke AG, Vasey DP, Symonds EM, Faratian B, McLaughlin PJ, Price MR, Baldwin RW
Dept. Obstetrics and Gynecology, Univ. Hosp., Queen's Medical Centre, Nottingham NG7 2UH, England
Br J Obstet Gynaecol; 89(3):231-237 1982

Sera from patients with ovarian tumors were assayed for circulating immune complexes (CIC) by four well established assays based on the interaction of immune complexes with components of the complement system. There was no difference in control, pre- or post-operative or BCG-treated patients' sera. Levels were also unchanged in sera in antigen excess. In patients with ovarian tumors before the measurement of CIC would appear to be of little value as a screening test, as a guide to the extent of disease, prognosis or therapy. In a small pilot therapy-trial there was no difference in the survival rate between patients with Stage III and IV ovarian cancer treated with cyclophosphamide plus BCG and those who received only cyclophosphamide. Treatment with BCG was associated with postoperative pyrexia and a prolonged hospital stay. (Author abstract) (43 Refs)

43. HETEROGENEITY OF CIRCULATING IMMUNE COMPLEXES IN LUNG CANCER AND OTHER CHRONIC PULMONARY DISEASES (MEETING ABSTRACT)

Cooper KM, Moore M
Christie Hospital and Holt Radium Institute, Manchester, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

Circulating immune complex (IC) levels in sera from 58 healthy controls and a total of 212 patients with various chronic lung diseases including 74 with bronchial carcinoma were measured using three assays: Two complement-dependent assays (C1q fluid phase and Raji) and a complement-independent assay (L1210). The three assays generally revealed similar patterns of reactivity when control and pathological groups were compared but the L1210 assay invariably demonstrated the lowest incidence of positive values in each group. The most significant elevations in IC levels were exhibited in bronchiectasis (chronic bronchial suppuration) and bronchial carcinoma. However, within these two groups correlations between IC assay performed on individual sera were poor. Significant but weak correlations were only observed for C1q vs Raji in bronchiectasis and Clq vs L1210 in bronchial carcinoma. Complement-binding ICs were present to a similar extent in both conditions. However, non-complement binding ICs were found to be more common in bronchiectasis. (no Refs)

44. ABNORMAL IMMUNOREGULATION IN PATIENTS WITH NON-HODGKIN'S MALIGNANT LYMPHOMAS. I. INCREASED HELPER FUNCTION OF PERIPHERAL BLOOD T LYMPHOCYTES.

Gajl-Peczalska KJ, Chartrand SL, Bloomfield CD
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN, 55455
Clin Immunol Immunopathol; 23(2):366-378 1982

T lymphocytes isolated from the blood of 24 newly diagnosed and 2 relapsed patients with non-Hodgkin's malignant lymphomas were studied for helper/suppressor activity in cocultures with allogeneic tonsillar B lymphocytes stimulated with pokeweed mitogen. The IgA, IgG, and IgM secretion was measured by double-antibody radioimmunoassay. In 85% of patients with B lymphomas their T lymphocytes produced a severalfold increase in immunoglobulin secretion when compared with age-matched healthy controls. By contrast in two cases of T lymphoma, suppression of immunoglobulin secretion was observed. The ratio of 'T helper'/'T suppressor' lymphocytes, as measured with monoclonal antibodies (OKT4/OKT8), were similar for patients and controls, and concanavalin A-induced suppression was equally good. However, small numbers of patient T lymphocytes provided good help, while control cells failed in these higher dilutions. Possible explanations of the increased helper activity of 'nonmalignant' T lymphocytes in B lymphomas as related to clinical features and the pathogenesis of B- versus T-cell malignancies are discussed. (Author abstract) (31 Refs)

45. CORRELATION OF THE IMMUNE PROFILE WITH LOCAL IMMUNOCYTE INFILTRATION IN URINARY BLADDER TUMOURS.

Flamm J, Burkert S
Urologische Abteilung, Wilhelminenspital Wien, Montleartstrasse 37, A-1171 Wien, Austria
Urol Int; 37(1):61-67 1982

In 40 patients with urinary bladder tumors we compared the results of the immune profile, obtained by means of cutaneous tests with dinitrochlorobenzene (DNCB), and the infiltration of immunocompetent cells in the histological pattern after transurethral tumor resection. It was noted that the more the tumor had infiltrated, the less was it possible to immunize with DNCB or to achieve an immunocyte infiltration in the tumor. According to the classification of the WHO, there was a positive reaction in 56-67% and a correlating immunocyte infiltration in 50-73%. (Author abstract) (14 Refs) (In GER)

46. HETEROGENEITY OF MELANOMA-ASSOCIATED ANTIGENS DETECTED BY SERA FROM PATIENTS RECEIVING ADJUVANT ALLOGENEIC TUMOR VACCINE IMMUNOTHERAPY.

Dent PB, McCulloch PB, Liao SK, Stone BR, Singal DP
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Clin Immunol Immunopathol; 23(2):379-391 1982

Sera from 40 patients with malignant melanoma entered into a randomized controlled trial of nonspecific and specific active immunotherapy were studied for the presence of melanoma-specific IgG antibody. Reactivity was revealed by mixed hemadsorption assay against a panel of 10 cultured melanoma cell lines. Prior to therapy 3 of 40 patients had antibody to one or more melanoma lines which in all cases was eliminated by absorption with platelets or colon carcinoma cells. After 6 mo of therapy patients in the group not receiving tumor vaccine had no absorption-resistant antimelanoma reactivity. However all 10 patients receiving allogeneic tumor vaccine had high titered melanoma reactivity which in 8 patients was not removed by platelet or carcinoma absorption. Three patients reacted only against melanoma targets while of the remaining five patients, four reacted against cultured brain tumor cells supporting previous suggestions of a possible antigenic cross-reactivity among tumors of neuroectodermal origin. Clinical outcome was not correlated with the presence of antibody to melanoma target cells. Persistance of antibody was dependent on continued vaccine administration suggesting that rather than being an index of resistance, the presence of antibody may be a marker for the presence of tumor. Sera from alloimmunized melanoma patients identify a heterogeneous complex of melanoma-associated surface antigens. More information about the serological and immunological properties of these antigens is required to determine if these responses are clinically relevant. (Author abstract) (21 Refs)

47. THE EPIDEMIC OF ACQUIRED IMMUNE DYSFUNCTION IN HOMOSEXUAL MEN AND ITS SEQUELAE. OPPORTUNISTIC INFECTIONS, KAPOSI'S SARCOMA, AND OTHER MALIGNANCIES: AN UPDATE AND INTERPRETATION.

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Cancer Treat Rep; 66(6):1391-1395 1982

Incidence of pneumocystis carinii pneumonia (PCP) and Kaposi's sarcoma (KS), survival, risk factors, immune dysfunction, genetics, course of the illness, and treatment are reviewed. Three-hundred patients (290 men) with a new syndrome have been reported; 135 had CP, 115 KS, 28 both diseases, and 22 other opportunistic infections. The mortality rate has been 40%; however, greater than 70% of patients with earliest diagnosed cases have died. Eighty-five percent of the 300 patients have been less than 45 yr old, with a median of 35 yr. Of the 290 men, 242 have been homosexual or bisexual. Ninety-eight percent of the homosexual male patients have had a history of exposure to nitrites, mainly amyl or butyl inhalants, but no one nitrite preparation is over-reported, suggesting that whatever the involvement of nitrites in the syndrome is not due to a contaminant. A very extensive case-control study will be required to sort out the relative contributions of nitrites and transmissible microbes; independent risk factors may be impossible to be identified. The breadth of immune defects observed in the syndrome explains the broad gap in host defenses against all classes of microbes that are associated with cellular immunity. The possibility exists that once the patients have become immunodeficient, a considerable reactivation of the cytomegalovirus infection occurs. As many as one third of KS patients in the epidemic appear to be developing other malignancies, as occurs with other KS patients, including the sporadic and endemic patients and the patients in renal transplant recipients or in patients receiving chronic immunosuppressive therapy. (17 Refs)

48. MONONUCLEAR-CELL INFILTRATION IN OVARIAN CANCER. II. IMMUNE FUNCTION OF TUMOUR AND ASCITES-DERIVED INFLAMMATORY CELLS.

Haskill S, Koren H, Becker S, Fowler W, Walton L
Dept. Obstetrics and Gynecology, Univ. North Carolina, Chapel Hill, NC, 27514
Br J Cancer; 45(5):737-746 1982

Mononuclear cell fractions were isolated from blood, ascites and solid tumors of patients undergoing surgery for Stages III and IV adenocarcinoma of the ovary, and evaluated for their response in NK, ADCC and PHA assays. Control experiments with the same fraction of normal blood indicated that these responses were not influenced by the enzymes used to isolate the tumor and ascites inflammatory cells. The inflammatory cell fractions isolated from both tumor sites which sedimented in the velocity range of blood mononuclear cells were adequate in number and composition for comparison with similar cells from blood. E RFC values in both ascites and tumor fractions exceeded those of patient blood. However, there was a marked difference in distribution of the T subsets between blood, ascites and tumor, which could cause the variable test results between the different cell sources. PHA responses of patient blood and ascites fractions were about half that of normal blood. Tumor-infiltrating lymphocytes (TIL) were less than 10% as responsive as normal blood. The depressed PHA responses of the TIL were not due to the presence of a suppressor cell population. NK activity of patient blood was less than that of normal blood, but not as much as the ascites or TIL cells. The activity of the ascites-derived lymphocytes was enhanced by treatment with interferon. ADCC activity against both CRBC and SB cells was normal or higher than controls in patient blood, and depressed in the ascites-derived fractions. TIL responded to less than 10% of the patient blood values. The results indicate a lack of response by ascitic and TIL cells in assays dependent on FcR-bearing effector cells and a greater loss of PHA-reactive cells from the tumor than from blood and ascites. These data could result from intratumor inactivation, or a failure of the particular subset to localize either in the ascites or the tumor site. (Author abstract) (32 Refs)

REVIEWS

49. MONOCLONAL ANTIBODIES IN ONCOLOGY.

Sikora K
Ludwig Inst. Cancer Res., Medical Sch., Hills Road, Cambridge CB2 2QH, England
J Clin Pathol; 35(4):369-375 1982

Molecular biology has made tremendous strides over the last 5 yr. The new biology allows us to prepare monoclonal antibodies to defined antigens; to detect, isolate and clone specific genes; and to insert these genes into defined sites in different cells giving new functions to old organisms. These revolutionary developments have been followed closely by researchers, businessmen, politicians and philosophers, as well as by those involved in the clinical care of patients. Although our understanding of human molecular biology is increasing rapidly, it is the development of monoclonal antibodies that has the most immediate application in the clinic. There have been several reports of their use in the diagnosis, localization and treatment of human malignant disease. This review describes developments that are likely to have direct relevance to patient care in the near future. (Author abstract) (32 Refs)

50. IMMUNE COMPLEXES: CHARACTERISTICS, CLINICAL CORRELATIONS, AND INTERPRETIVE APPROACHES IN THE CLINICAL LABORATORY.

Ritzmann SE, Daniels JC
Dept. Pathology, Baylor Univ. Medical Center, Dallas, TX, 75246
Clin Chem; 28(6):1259-1271 1982

Immune-complex-mediated injury is thought to play a role in diseases such as rheumatoid arthritis, systemic lupus erythematosus, serum sickness, various infectious diseases, and malignancies. With increased appreciation of the biological and pathological significance of circulating immune complexes has come efforts to develop appropriate techniques for identifying and measuring them. Common approaches exploit such phenomena as the attachment of complement components to antigen-antibody complexes, the presence of specialized receptors for immune complexes at the surface of cells, and the ability of rheumatoid factor to bind with immune complexes has yielded abstruse results in numerous human pathological conditions. Unfortunately, these results seldom correlate with one another in a given disease. Thus, use of a panel of immune complex assays has been recommended. Indirect consequences of immune complex disease may still be appraised and evaluated with some confidence in clinical medicine: measurements of C3 and C4, cryoglobulins, serum viscosity, and turbidity of serum samples. Measurement of immune complexes may be useful in diagnosis, prognosis, and therapeutic monitoring, but it is the characterization of immune complexes that holds the greatest potential for better understanding of disease mechanisms. (Author abstract) (88 Refs)

51. IMMUNOLOGICAL INVESTIGATION AND IMMUNOTHERAPY IN PATIENTS OPERATED ON FOR BREAST CARCINOMA.

Reynier J, Villet R, Bazin JC, Bizzini B, Gandrille C, Guettier C, Henocq E, Hollmann K, Mogenet M, Pompidou A, Santus JP, Verley JM
Hoptital Boucicaut, 78 rue de la Convention, 75015 Paris, France
Int Surg; 67(1):17-24 1982

The tumor-host relationship is an essential factor in the onset, development, and recovery from malignancies. A basic consideration in the treatment of cancer patients must therefore be to understand this relationship and attempt to modify it in order to favor the host. We here discuss the results of a study of the immunologic status of 91 breast cancer patients. The use of a battery of tests with five subcutaneous hypersensitivity antigens allowed us to detect some differences in the immunological profiles of patients with or without lymph node involvement. The effect of an immunostimulant fraction prepared from Corynebacterium granulosum, P40 is also analyzed. This fraction significantly modifies tumoral recurrence in DMBA-induced mammary cancers in the Sprague Dawley rat, causes regression of mammary permeation nodules following in situ injection and modifies the cutaneous reactions of one-half of the anergic breast cancer patients although regular re-challenge is still necessary. (Author abstract) (43 Refs)

52. MECHANISMS OF MACROPHAGE-MEDIATED TUMOR CYTOLYSIS.

Key ME, Hoyer L, Bucana C, Hanna MG, Henkart P, Goldfarb R, Herberman R, Zagury D, Berke M
Cancer Metastasis and Treatment Lab., NCI-Frederick, Cancer Res. Facility, Frederick, MD, 21701
Adv Exp Med Biol; 146(82):265-310 1982

Mechanisms of macrophage-mediated cytotoxicity against two very different kinds of tumors, the T1699 mammary adenocarcinoma of DBA/2 mice and the L10 hepatocarcinoma of strain 2 guinea pigs are reviewed. In both of these systems, tumor regression can occur in vivo; T1699 tumor often undergoes spontaneous regression, while the L10 tumor can be induced to regress following immune stimulation of tumor-bearing animals. Macrophages contained within T1699 tumors can kill tumor cells by both intracellular and extracellular processes, whereas macrophages from guinea pigs immunotherapeutically cured of L10 tumors kill exclusively by extracellular means. Similarities between the antimicrobial and antitumor properties of macrophages are discussed. Interactions of PM and L10 tumor cells were examined in vitro by electron microscopy and a marked increase in the binding to tumor cells of macrophage obtained from BCG-treated guinea pigs compared to those obtained from normal guinea pigs were observed. A major difference between the macrophage-tumor cell interactions of BCG-tumor-cured and normal guinea pigs is the presence of electron-dense bodies in the intercellular space between L10 cells and macrophage from BCG-tumor-cured animals. In the two tumor systems studied target cell-to-effector cell contact preceded the cytotoxic event, lysosomes within macrophages were polarized toward tumor cells, and macrophages spread over tumor cell surfaces and then destroyed the tumor cell indicating that the subcellular mechanism is the same despite the apparently different methods of killing. (80 Refs)

53. INTERFERON THERAPY.

World Health Organization Scientific Group on Interferon Therapy
World Health Organization, Geneva, Switzerland
WHO Tech Rep Ser (676): 28 pp., 1982.

Recent advances in interferon (IFN) production and clinical effects are reviewed. Production of human IFN (human interferon alpha, human interferon-beta, human interferon-gamma) with WBC and viruses, B-lymphoblastoid cells and virus, fibroblasts and double-stranded RNA, or a combination of WBC or T-lymphoblastoid cells with mitogen is described. Use of bacteria and yeast for producing IFN by recombinant techniques is relatively low in cost. Origin of human blood cells and cultured human cells used for IFN production, production and purification processes, and the possibility of longe-term consequences of IFN therapy must be carefully monitored. Standardization and measurement of biological activity is discussed. IFN have been beneficial in treating herpetic keratitis, herpes zoster, and laryngeal papilloma. IFN in combination with antiviral drugs may be useful for patients with chronic hepatitis B infections. In malignant disease, complete tumor regression has rarely been reported with IFN, although objective improvements have been seen in cases with multiple myeloma, disseminated follicular lymphoma, and recurrent breast cancer with systemic IFN. Occasional responses have been reported with other tumors. Use of IFN for treatment of malignant disease in man remains experimental and its clinical benefit is not proven. The max tolerated dose and the biologically effective dose must be defined for different tumors. (26 Refs)

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CLINICAL TRIALS

1. TREATMENT OF LEUKEMIA AND LYMPHOMAS WITH INTERFERONS. I. TREATMENT OF MYELOMAS WITH HUMAN INTERFERON B.

Misset JL, Mathe G, Gastiaburu J, Goutner A, Dorval T, Gouveia J, Hayat M, Jasmin C, Schwarzenberg L, Machover D, Ribaud P, DeVassal F, Horoszewicz JS
Service des Maladies Sanguines et Tumorales, Institut de Cancerologie et d'Immunogenetique, 12-16 avenue Paul-Vaillant-Couturier, 94800 Villejuif, France
Biomedicine; 36(1):55-59 1982

Eighteen patients with malignant gammopathies (16 with myeloma and 2 with Waldenstrom's disease) for a short time because in a Phase II-I trial were treated with human (IF beta) given iv 6 x 10(6) units weekly (7 patients) or 3 x 10(6) units twice weekly (11 patients) during at least 3 months if tolerated. Treatment was discontinued because of side-effects in three patients. Reduction of the M component of at least 25% from the initial value was obtained in three patients. In one case, was also observed the disappearance of a urinary Bence-Jones protein, in four cases a significant reduction of bone marrow infiltration by plasma cells and, in five cases, major alleviation or

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disappearance of bone pain. Length of treatment seems an important factor for activity. Immune monitoring with currently available tests, mainly NK cell activity, yielded no correlation with therapeutic effect in these patients. This very preliminary study demonstrates the effect of fibroblastic interferon in myeloma, but further studies are mandatory to determine the population of patients likely to benefit from treatment, the best modalities, possible special indication, dose schedule and duration of treatment. Interferon, however, already appears in this population of patients as giving results similar to those of single agent chemotherapy. As it is not myelosuppressive, it could be indicated in that frequent situation of advanced myeloma with bone marrow failure contraindicating combination chemotherapy. (Author abstract) (23 Refs) (In FRE)

2. LEUKOCYTE-DERIVED INTERFERON (ALPHA) IN HUMAN BREAST CARCINOMA. THE AMERICAN CANCER SOCIETY PHASE II TRIAL.

Borden EC, Holland JF, Dao TL, Gutterman JU, Wiener L, Chang YC, Patel J
K4/414, Wisconsin Clin. Cancer Center, 600 Highland Ave., Madison, WI, 53792
Ann Intern Med; 97(1):1-6 1982

A multi-institutional trials program was initiated to define the effects of interferons in disseminated human breast carcinoma. Interferon alpha, prepared from buffy coats, was administered intramuscularly at 3 X 10(6) U daily for an initial period of 28 days. Of 23 patients who entered the program, five had an objective partial response of 92 days mean duration at diverse sites of involvement. Patients who responded were significantly older ($p = 0.050$) than nonresponders. Dose escalation in eight patients did not result in any clear evidence of additional responses. Major toxicities were fatigue, anorexia with weight loss, and reversible leukopenia (less than 3.5 X 10(9) leukocytes/L in 16 patients). Natural killer cell and antibody-dependent cell-mediated cytotoxicity were significantly (p less than 0.05) enhanced 48 hr after interferon administration began but subsequently declined despite continued therapy. Serum beta2-microglobulin concentrations increased on Day 15 (p less than 0.05) and remained significantly elevated on Day 22 (p less than 0.005). Peak interferon titers (mean, 62 U) occurred 6 hr after interferon was started, varied widely between patients, and were higher and more persistent with dose escalation. Once an optimal dose is defined, prospectively randomized trials will define what role interferons may have in systemic therapy of breast carcinoma. (Author abstract) (29 Refs)

3. A RANDOMIZED STUDY OF COMBINATION CHEMOTHERAPY (VAC-FMC) WITH OR WITHOUT IMMUNOSTIMULATION BY CORYNEBACTERIUM PARVUM IN METASTATIC BREAST CANCER.

Fritze D, Becher R, Massner B, Kaufmann M, Bruntsch U, Gallmeier WM, Mayr AC, Drings P, Abel U, Edler L, Jungi WF, Queisser W, Senn HJ
Med. Univ.-Klinik, Bergheimer Str. 58, D-6900 Heidelberg, W. Germany
Klin Wochenschr; 60(12):593-598 1982

A total of 156 patients with metastatic breast cancer were entered into a prospective multicenter trial in September 1975. All patients were treated monthly with vincristine, adriamycin and cyclophosphamide (VAC) six times, followed by 5-fluorouracil, methotrexate and cyclophosphamide (FMC) until progression was documented. By random assignment, the patients received 5 mg/m2 Corynebacterium parvum (CP) subcutaneously on Day 1, in addition to VAC/FMC. Of the 150 evaluable patients, 33 of 76 (45%) and 36 of 74 (49%) had complete or partial response to VAC/FMC plus CP, respectively. The Kaplan-Maier curves of duration of remission and survival were almost identical (medians 14.5 vs 12.1 mo and 22.2 vs 21.1 mo, respectively). The hematologic and gastrointestinal toxicity were also similar in the two study groups. However, 19 of 74 (26%) patients developed skin ulcers after repeated injections of CP. These patients showed prolonged survival ($p = 0.002$, log rank test). These results suggest that adding nonspecific immunostimulation with CP to currently available chemotherapy on Day 1 is of no benefit to most patients with metastatic breast cancer, but may select an 'immunoreactive' subgroup with increased local toxicity and survival. (Author abstract) (12 Refs)

4. LEVAMISOLE AS AN ADJUVANT TO CHEMOTHERAPY IN EXTENSIVE BRONCHOGENIC CARCINOMA. A VETERANS ADMINISTRATION LUNG CANCER GROUP STUDY.

Davis S, Mietlowski W, Rohwedder JJ, Griffin JP, Neshat AA
Veterans Admin. Medical Center, East Orange, NJ, 07019
Cancer; 50(4):646-651 1982

A randomized trial of 381 patients with extensive lung cancer compared immunochemotherapy with levamisole (150 mg/m2 orally 3x a wk), cyclophosphamide (700 mg/m2 IV every 3 wk) and lomustine (CCNU, 70 mg/m2 orally every 6 wk) with the same chemotherapy without levamisole. When disease progressed, doxorubicin hydrochloride or doxorubicin hydrochloride plus levamisole was used. Hematologic toxicity required reduction of the levamisole dosage to 2.5 mg/kg (100 mg/m2) 3x a wk, every other wk. When corrections are made for all variables, levamisole itself had a negative influence on survival. Patients given 150 mg/m2 had a shorter median time to treatment failure ($p = 0.02$), lower response rate ($p = 0.02$), more toxicity ($p = 0.08$), and shorter median survival ($p = 0.08$). Patients with 10% or greater weight loss had significantly shorter survival ($p = 0.006$). The regimen with the reduced dosage of levamisole also was more toxic ($p = 0.05$) but otherwise did not differ from the control regimen. The cause of the adverse effect of levamisole is unknown. It did not occur because of an excess of toxic deaths or because smaller doses of cytotoxic drugs were given to patients treated with levamisole. Neither the initial lymphocyte count nor the Candida skin test reactions had a significant effect on the study endpoints when correction was made for dominant prognostic factors such as the initial performance status and weight loss. (Author abstract) (26 Refs)

5. CYCLOSPORIN A AS PROPHYLAXIS AGAINST GRAFT-VERSUS-HOST DISEASE IN 36 PATIENTS.

Barrett AJ, Kendra JR, Lucas CF, Joss DV, Joshi R, Pendharkar P, Hugh-Jones K
Westminster Bone Marrow Transplant Team, Westminster Medical Sch., Children's Hosp., London, England
Br Med J; 285(6336):162-166 1982

Oral cyclosporin A was used as prophylaxis against graft-versus-host disease in (a) 31 patients with acute leukemia or aplastic anemia given transplants of HLA-matched bone marrow and (b) five patients with inborn errors of metabolism given transplants of haplotype-identical (parental) bone marrow. Twenty-six patients survived longer than 2 months after the operation. Despite the cyclosporin A, 31 patients (86%) suffered an acute form of graft-versus-host disease and 22 (61%) a chronic form. Nevertheless, the disease was usually treatable with immunosuppressive agents and caused the death of only one patient. Cyclosporin A caused renal toxicity in all cases; occasionally this was associated with a 'capillary leak' syndrome, fatal in two patients. In children hypertension, fits, and fluid retention were common side effects. Blood concentrations of cyclosporin A correlated with blood urea values and blood pressure but did not predict the occurrence of graft-versus-host disease. Four different dose schedules were used to find the optimum way to administer the drug. Oral cyclosporin A is extremely effective at reducing the severity of graft-versus-host disease, but prevention of the disease is limited by toxicity of the drug and variable absorption. Better results might be achieved with parenteral administration or by using the drug in combination with other methods. (Author abstract) (15 Refs)

6. EFFECT OF ADOPTIVE IMMUNOTHERAPY USING BONE MARROW TRANSPLANTATION AND THYMOSTIMULIN ON IMMUNITY IN CANCER PATIENTS.

Grinevich IuA, Kamenets LIa, Ganul VL, Okulov LV, Kogut GI, Glukhen'kaia GT
Res. Roentgenoradiological and Oncological Inst., Kiev, USSR
Klin Khir; (5):33-36 1982

The efficacy of adoptive immunotherapy was evaluated in 40 patients with Stage III esophageal cancer and in 142 with cancer of the proximal region of the stomach. The patients received preoperative radiotherapy (500 rads/day, total dose 2,500-3,000 rads) and surgery. Within 2-3 wk after the surgery, the patients received transplantation of autologous bone marrow preincubated with thymostimulin. The preoperative therapy and surgery resulted in a marked decrease in lymphocyte count. The bone marrow transplantation did not affect the count of rosette-forming cells or the index of lymphocyte migration in the presence of autologous plasma; it did, however, enhance production of IgA and IgG. Transplantation of bone marrow preincubated with thymostimulin brought about more effective normalization of the indices of cellular and humoral immunity than transplantation of bone marrow that was not preincubated with the thymostimulin. (12 Refs) (In RUS)

7. CYTOMEGALOVIRUS IMMUNE PLASMA IN BONE MARROW TRANSPLANT RECIPIENTS.

Winston DJ, Pollard RB, Ho WG, Gallagher JG, Rasmussen LE, Huang SN, Lin CH, Gossett TG, Merigan TC, Gale RP
Div. Infectious Diseases, Dept. Medicine, Univ. California Los Angeles Center for Health Sciences, Los Angeles, CA, 90024
Ann Intern Med; 97(1):11-18 1982

The effects of passive immunization on cytomegalovirus infection and interstitial pneumonia in marrow transplants were evaluated in a randomized, controlled trial. Twenty-four patients received cytomegalovirus immune plasma before and after transplantation, and 24 patients were controls. Although the incidence of cytomegalovirus infection was similar in the control and plasma groups, symptomatic infection (12 of 24 versus 5 of 24, $p = 0.07$) and interstitial pneumonia (11 of 24 versus 5 of 24, $p = 0.12$) occurred less frequently in the group receiving plasma. Cytomegalovirus infection occurred in 11 of 13 recipients of leukocyte transfusions and in 16 of 35 patients not given leukocyte transfusions ($p = 0.02$). Among patients not given leukocyte transfusions, the incidence of cytomegalovirus infection was similar in the control and plasma groups, but symptomatic infection (8 of 18 versus 1 of 17, $p = 0.03$) and interstitial pneumonia (9 of 18 versus 1 of 17, $p = 0.01$) were significantly less in the group receiving plasma. These results suggest that passive immunization modifies cytomegalovirus infection in humans and prevents interstitial pneumonia in marrow transplants, especially when leukocyte transfusions are not used. (Author abstract) (39 Refs)

8. TREATMENT OF CYTOMEGALOVIRUS PNEUMONIA AFTER MARROW TRANSPLANT WITH COMBINED VIDARABINE AND HUMAN LEUKOCYTE INTERFERON.

Meyers JD, McGuffin RW, Bryson YJ, Cantell K, Thomas ED

Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA, 98104

J Infect Dis; 146(1):80-84 1982

Seven marrow transplant recipients were treated with human leukocyte interferon and vidarabine for cytomegalovirus pneumonia. Although the mean virus titer in biopsy and autopsy lung specimens from five patients decreased from 5 X 10(4) to 1 X 10(2) 50% tissue culture infective doses, there was little clinical evidence of efficacy and only one patient survived. Treatment was stopped in four patients because of declining neutrophil counts, and two of these four patients also showed severe neurotoxicity. The combination of these agents was neither safe nor effective for the treatment of cytomegalovirus pneumonia after marrow transplantation. (Author abstract) (15 Refs)

SYNTHETIC IMMUNOTHERAPEUTIC AGENTS

9. CHEMO-IMMUNOTHERAPY OF METHYLCHOLANTHRENE-INDUCED FIBROSARCOMA BY CONCANAVALIN A-BOUND TUMOR VACCINE, LEVAMISOLE AND MITOMYCIN C.

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J Pharmacobio Dyn; 5(4):245-251 1982

The feasibility of combined immunotherapy by tumor vaccine and levamisole (LEV) with mitomycin C (MMC) against a 3-methylcholanthrene induced murine fibrosarcoma was investigated. Concanavalin A (ConA)-bound MMC treated (100 mg/ml) fibrosarcoma cell antitumor vaccine had immunoprophylactic potency showing perfect resistance to a challenge of 10(5) fibrosarcoma cells. ConA-free MMC-treated vaccine was much less potent. LEV combined with the vaccine augmented the therapeutic effect of the vaccine. While 27% of mice treated with ConA-bound MMC vaccine were cured (80 day survival), 62% treated with the same regimen plus LEV (10 mg/kg/day) were cured. No enhancing effect was observed when LEV was administered before or 3 days after chemotherapy. The most beneficial therapeutic regimen was a chemo-immunotherapy by vaccine and MMC combined with LEV administered just after the vaccination. (10 Refs)

10. ENHANCING ACTIVITY OF VARIOUS IMMUNOAUGMENTING AGENTS ON THE DELAYED-TYPE HYPERSENSITIVITY RESPONSE IN MICE.

Bartocci A, Read EL, Welker RD, Schlick E, Papademetriou V, Chirigos MA

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Cancer Res; 42(9):3514-3518 1982

Six immunoaugmenting agents were tested in the delayed-type hypersensitivity reaction (DTH) in normal BALB/c x DBA/2 mice. The agents tested, levan, lentinan, mannozym, maleic anhydride divinyl ether, polyriboinosinic-polycytidylic acid-poly-L-lysine, and highly purified L-cell interferon, gave significant increases in the DTH response above the sheep red blood cell control. The schedule of doses for each agent corresponded with previous experiments from this laboratory of the maximum natural killer cell activity, macrophage activation, and interferon induction. Highly purified L-cell interferon was capable of eliciting a significant DTH response when given 4 hr after the initial challenge with sheep erythrocytes. In addition, lambda-carrageenan, a macrophage-cytotoxic agent which can render the macrophage inactive, was found to suppress the DTH response to levels slightly above phosphate-buffered saline controls. The carrageenan-induced suppression of the DTH response could be abrogated by coadministration with immunoaugmenting agents to levels attained with the immunoaugmenting agents alone. (Author abstract) (32 Refs)

11. REGULATION OF HUMAN NATURAL KILLING BY LEVAMISOLE.

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Cancer Immunol Immunother; 13(1):24-29 1982

Effect of levamisole (LE) on human natural killing (NK) activity was studied in vitro. LE at concentrations greater than 10(-4) M clearly inhibited NK activity. Peripheral blood leukocytes (PBL) were pretreated with LE for 18 hr, washed free of the reagent, and then tested for NK activity. PBL pretreated with LE at concentrations greater than 10(-4) M again showed decreased NK activity, even though LE was not present during the NK assay suggesting that LE inhibited NK by decreasing effector cell activity, without affecting target cell susceptibility. The susceptibility of K562 to killing by complete medium (CM)-treated PBL or LE-treated PBL was, however, unaffected by LE treatment. The kinetics of effector cell inactivation was assessed by preincubating several aliquots of the same PBL effector cell preparation for a total period of 16 hr. Results of the experiment showed that greater than 4 hr was required to inactivate NK effector cells, if the activity was subsequently tested in the absence of the drug. Presence of 10(-3) M LE throughout the entire culture period depressed PBL response to phytohemagglutinin (PHA) stimulation. A 19-hr pretreatment with a subsequent wash had no effect on the response to PHA, while NK activity was greatly suppressed by the treatment. PBL were pretreated with LE and cultured in CM. PBL preincubated with 10(-3) M LE for 8 hr showed suppressed NK activity, as expected, when tested immediately after the preincubation. When the inactivated effector cells were incubated further for an additional 16 hr, the activity recovered to near-normal level. Therefore, the inactivation was reversible. (31 Refs)

12. KINETIC STUDIES OF THE IMMUNOPHARMACOLOGIC EFFECTS OF NPT 15392 IN MICE.

Florentin I, Taylor E, Davigny M, Mathe G, Hadden JW
Hopital Paul-Brousse, Institut de Cancerologie et d'Immunogenetique, 14 avenue Paul Vaillant-Couturier, 94804 Villejuif, France
Int J Immunopharmacol; 4(3):225-234 1982

The immunopharmacological activities and kinetics of host response following a single injection of NPT 15392 (9-erythro-(2-hydroxy,3-[9-erythro-(2-hydroxy,3-nonyl) hypoxanthine; ip .1 mg/kg] in normal BALB/c mice were investigated. NPT 15392 modified immune function for at least 14 days after a single administration. Both T-dependent and T-independent antibody production were increased, and differences in the kinetics of the responses implied different mechanism which might include actions on T helper cells, B cells, and macrophages. NPT 15392 increased the response of spleen cells to stimulation with dextran sulfate, a macrophage-dependent B cell response, and suppressed that to phytohemagglutinin, a macrophage-dependent T-cell response. Cytocidal activity of natural killer cells and T killer cells were increased without affecting antibody-dependent cytotoxicity. NPT 15392 increased the delayed hypersensitivity response to immunization with oxazolone. These results suggest that NPT 15392 may have value in cancer immunotherapy. (12 Refs)

13. POTENTIATED IMMUNE RESPONSES AFTER ADMINISTRATION OF ACLACINOMYCIN.

Orbach-Arbouys S, Andrade-Mena CE, Berardet M, Mathe G
Hopital Paul-Brousse, Institut de Cancerologie et d'Immunogenetique, F-94804 Villejuif Cedex, France
Int Arch Allergy Appl Immunol; 68(2):117-121 1982

After the intraperitoneal injection of aclacinomycin into mice, a variety of immune responses were increased. The total plaque-forming spleen cell response to SRBC was higher in treated animals than in controls, in spite of an apparent cytotoxic effect on B cells. The aclacinomycin-sensitive cell is apparently a long-lived cell, surviving adult thymectomy. Delayed-type hypersensitivity reactions were also augmented in treated animals, particularly those bearing tumors. In adjuvant-treated mice, the injection of aclacinomycin augments the immune response still further. Such observations should be taken into account in the establishment of clinical protocols associating immunotherapy and chemotherapy. (Author abstract) (17 Refs)

INTERFERON

14. INTERFERON INDUCTION AND THERAPY OF BRAIN TUMORS IN RATS BY POLY(ICLC).

Machida H, Takezawa J, Kuninaka A, Yoshino H, Nakamura O, Takakura K
Res. Labs., Yamasa Shoyu Ltd., Choshi, Chiba 288, Japan
Microbiol Immunol; 26(4):353-358 1982

Comparative interferon-inducing and antitumor activities of poly(ICLC) and poly(I)poly(C) were studied in male SD rats and in female Wistar rats with intracerebrally transplanted glial tumors. The preparation containing 1 mg of poly(I)poly(C) and 0.5 mg of poly-L-lysine (poly(ICLC)-B) and the preparation containing 1 mg of poly(I)poly(C) and 0.75 mg of poly-L-lysine (poly(ICLC)-A) had the higher melting temperature and greater resistance to human RNase than the parental poly(I)poly(C). The levels of plasma interferon after injection of poly(ICLC)-A was lower than those after injection of poly(ICLC)-B or poly(I)poly(C). Poly(ICLC)-B induced more prolonged elevation of plasma interferon titers than poly(I)poly(C). Treatment with poly(ICLC) prevented the loss of body wt and increased the life-span of rats bearing glial tumors. The antitumor activity of poly(ICLC) was correlated with persistence of the high level of plasma interferon. Treatment with poly(ICLC)-B (0.5 mg/kg, 3x/wk) was as effective as the treatment with aminochloroethyl nitrosourea (5 mg/kg). (14 Refs)

15. SUSCEPTIBILITY OF HUMAN LEUKAEMIAS TO CELL-MEDIATED CYTOTOXICITY BY INTERFERON-TREATED ALLOGENEIC LYMPHOCYTES.

Moore M, Taylor GM, White WJ
Paterson Laboratories, Christie Hosp. and Holt Radium Inst., Whithington, Manchester, England
Cancer Immunol Immunother; 13(1):56-61 1982

Susceptibility to spontaneous cell-mediated cytotoxicity (CMC) of 22 human leukemias (13 acute myeloid, 9 lymphoid) by exogenous interferon (IFN)-treated and untreated lymphocytes from 24 unrelated normal donors was determined in eight experiments. Each leukemic target cell was tested with effectors from a minimum of 3 and a max of 11 donors, in parallel with tests on the K562 erythroleukemia line. In one experiment, CMC on the leukemias was demonstrable in two (E77, E79) of the four tested, as judged by evidence of amplification of cytotoxicity by IFN-treated effectors, compared with untreated peripheral blood lymphocytes, and a dose-response relationship over three effector-to-target (E:T) ratios tested. Considerable variation in the level of IFN-induced amplification was observed against both the cell line (E:T ratio 20:1) and the fresh targets (E:T ratio 40:1). The widest differences between IFN-amplified killing (IAK) and unstimulated CMC were found on E72 (25%), E76 (29%), and E84 (31%) among the myeloid leukemias, and E77 (32%) and E79 (29%) among the lymphoid leukemias. However, the level of IAK on the leukemias was almost without exception lower than that on K562 cells. Only 1/22 leukemias gave positive CMC (greater than 10%) with one or more donor lymphocytes without IFN pretreatment, compared with 10 with IFN pretreatment. Out of the total of 116 effector:leukamia cell combinations tested, one was positive without IFN, as against 22 that were positive with IFN. Seven leukemias were susceptible to IAK by more than one donor. No correlation between susceptibility to IAK, the morphological type of leukemia, and the induction of remission in those patients was observed. (38 Refs)

16. DIRECT CYTOLYSIS BY PARTIALLY-PURIFIED PREPARATIONS OF IMMUNE INTERFERON.

Tyring S, Klimpel GR, Fleischmann WR, Baron S
Dept. Microbiology, Univ. Texas Medical Branch, Galveston, TX, 77550
Int J Cancer; 30(1):59-64 1982

Mouse interferon-gamma preparations purified 30-fold were found to have direct cytolytic activity against a number of tumor and normal cells. Cell killing was determined using a sensitive, rapid and accurate assay which employed very low numbers of cells and very small quantities of interferon. The cytolytic activity of IFNgamma on 11 murine tumor cell lines was investigated. A 20-fold difference was found between the most sensitive cell type, P-388 lymphoma, versus the most resistant cell type, C127v leukemia. A number of normal mouse cells was also found to have low to intermediate sensitivity to the cytolytic action of IFNgamma. Human IFNgamma was also shown to have cytolytic activity which, like mouse IFN-gamma, was relatively species-specific. Direct cytolysis was not found to be a characteristic of IFN-alpha/beta. Different mechanisms of action for the antiviral and cytolytic activities of IFNgamma are indicated because the cytolytic titer of IFN-gamma did not parallel its antiviral titer on most cell types and increasing the cell number produced a decrease in the cytolytic titer and an increase in the antiviral titer. High concentrations of IFNgamma (ie, 2,900 units/ml) resulted in complete lysis of cells within 24 hr, while lower concentrations (ie, 700 units/ml) resulted in a reversible inhibition of cell growth during this time period. Evidence that the cytolytic substance in the IFN-gamma preparation was IFNgamma include the following: (1) both antiviral and anticellular activities copurified through a 30-fold purification; and both activities were (2) relatively species-specific; (3) sensitive to heat; (4) inactivated by low pH and (5) neutralized by antibodies to IFNgamma. Therefore, we propose the possibility that direct cytolysis is yet another of IFNgamma's distinctive activities. (Author abstract) (29 Refs)

17. INTERFERON ENHANCEMENT OF THE INVASIVE CAPACITY OF EWING SARCOMA CELLS IN VITRO.

Siegal GP, Thorgeirsson UP, Russo RG, Wallace DM, Liotta LA, Berger SL
(c/o Berger) Lab. Pathophysiology, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(13):4064-4068 1982

The ability of interferons to reduce cell proliferation in vitro and in vivo is a well-studied phenomenon. To extend such observations, the effect of interferons on the invasiveness in vitro of human malignant cells derived from a Ewing sarcoma was evaluated. Two related parameters were examined: (i) production of Type IV (basement membrane) collagenase and (ii) penetration of human amnion basement membrane and collagenous stroma. After 6 days of treatment with crude fibroblast interferon, leukocyte interferon, or lymphoblastoid interferon at 100 units/ml in serum-free medium, Type IV collagenase levels increased two- to four-foid per cell relative to those of untreated controls. With homogeneous fibroblast and lymphoblastoid interferons, a two-fold elevation in Type IV collagenase was detected after 2 days, with further increases, occasionally dramatic, occurring on the 4th and 6th day of treatment. The ability of Ewing sarcoma cells to invade human amnion connective tissue was measured after 6 days of treatment with various interferons. Relative to the behavior of untreated controls, crude leukocyte interferon, homogeneous lymphoblastoid interferon, and homogeneous fibroblast interferon at 100 units/ml augmented invasiveness 3-, 17-and 22-fold, respectively, when cells were allowed 4 days in which to traverse the amnion. When untreated cells were exposed simultaneously to the amnion and to homogeneous lymphoblastoid or fibroblast interferon, a four- to five-fold increase in invasiveness above control levels was observed in 2 days. These data emphasize the complexity of interferon-induced phenomena. In any overview, the effects of interferon on both the tumor cell and the host must be considered. (Author abstract) (27 Refs)

18. GROWTH STATE-SPECIFIC RESPONSIVENESS OF PRIMARY CULTURES OF A NUDE MOUSE-XENOGRAFTED HUMAN COLON CARCINOMA TO 4'-DEOXYDOXORUBICIN AND A CRUDE HUMAN LEUKOCYTE ALPHA-INTERFERON PREPARATION.

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Cancer Res; 42(9):3789-3792 1982

Improved procedures for the seeding of primary cultures from human colon tumors are described. Responsiveness of primary cultures from human colon carcinoma T348 to a crude preparation of human leukocyte alpha-interferon and a DNA-intercalating experimental anticancer drug, 4'-deoxydoxorubicin, has been investigated. The effect of the interferon preparation on such cultures is shown to be growth state specific; ie, stationary populations are killed, whereas fast-growing cultures are reversibly growth inhibited by the same doses of interferon. In contrast, 4'deoxydoxorubicin kills growing populations, whereas stationary cultures are barely affected by the same concentration of this drug. Interferon antagonizes the cytotoxic effect of 4'deoxydoxorubicin on a growing colon tumor cell population when applied immediately after 4'-deoxydoxorubicin treatment. Implications of this finding for the combined application of several drugs in cancer therapy are discussed. (Author abstract) (11 Refs)

19. ROLE OF INTERFERON IN NATURAL KILL OF HSV-1-INFECTED FIBROBLASTS.

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J Immunol; 129(2):819-823 1982

The production of interferon during natural killer (NK) assays against HSV-1-infected fibroblasts (NK(HSV-1)) was studied to determine whether this interferon was responsible for inducing the preferential lysis of herpes-virus-infected target cells over uninfected target cells. The interferon produced during NK(HSV-1) assays was analyzed and found to have the properties of HU-IFN-alpha. Little or no IFN was produced during NK assays against uninfected fibroblasts (NK(FS)) or K562 (NK(K562)) cells. Although the appearance of interferon in the culture supernatants seemed to parallel the development of cytotoxicity during NK(HSV-1) assays, the levels of cytotoxicity and IFN generated did not correlate, arguing against a strict quantitative dependence of cytotoxicity upon IFN production. NK(K562) and NK(FS) cytotoxicity developed with little or no production of IFN. When IFN-pretreated effector cells were used, there was still a preferential lysis of infected over uninfected target cells. This preferential lysis by IFN-treated effector cells of infected over uninfected targets was seen as early as 2 hr into the assay. Anti-IFN antibodies added to the NK assays, although neutralizing all the IFN produced during the assays, had no effect on NK(FS) or NK(K562) cytotoxic activity and caused a slight reduction of NK(HSV-1) activity only in one of three experiments. We conclude that although IFN is generated during NK(HSV-1) assays, this IFN cannot solely account for the increased lysis of infected over uninfected cells and that NK(HSV-1) activity is in some other way dependent on the virus infection. (Author abstract) (34 Refs)

20. EFFECT OF HUMAN FIBROBLAST INTERFERON ON NATURAL KILLER CELL ACTIVITY: STIMULATION IN VITRO AND INHIBITION IN VIVO.

Heidemann E, Reichmann U, Wilms K, Treuner J, Niethammer D

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Klin Wochenschr; 60(12):625-629 1982

This paper describes the influence of human fibroblast interferon (IFN-beta) on the cytotoxic activity of natural killer cells (NK) in vitro and in vivo using the blood of healthy donors and myeloma patients. IFN-beta stimulates NK activity against all target cells tested in vitro in a dose-dependent way up to 250% of pretreatment values. At higher IFN concentrations, stimulation returned to baseline values. Stimulation was most pronounced in the lowest lymphocyte to target cell ratio. 1-to 2-h preincubation of effector cells with IFN was enough to achieve maximal stimulation. The effector cells of IFN-treated myeloma-patients, or patients with herpes zoster, showed a clear reduction of toxicity against all cells tested during the first infusion, as compared to the pretreatment values. (Author abstract) (22 Refs)

21. THE ROLE OF LIVER IN THE CATABOLISM OF HUMAN ALPHA- AND BETA-INTERFERON.

Bocci V, Pacini A, Bandinelli L, Pessina GP, Muscettola M, Paulesu L

Istituto di Fisiologia Generale Universita, 53100 Siena, Italy

J Gen Virol; 60(part2):397-400 1982

The susceptibility of human leukocyte alpha interferon, fibroblast beta interferon and recombinant alpha-2-interferon to clearance by the isolated and perfused rabbit liver has been evaluated. Human leukocyte and recombinant alpha-2-interferons were stable and their initial levels were maintained in the perfusate even if they had been treated with neuraminidase, thus suggesting that alpha-interferons have no exposed sugars recognizable by hepatic binding proteins. On the other hand, native, and particularly desialylated human beta-interferon, underwent marked hepatic uptake confirming the importance of the liver as a catabolic site for glycosylated interferons. (Author abstract) (21 Refs)

22. SEQUENTIAL ADMINISTRATIONS OF POLYRIBOINOSINIC ACID AND POLYCYTIDYLIC ACID INDUCE INTERFERON AND DEPRESS THE HEPATIC CYTOCHROME P-450-DEPENDENT MONOOXYGENASE SYSTEM.

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Biochem Biophys Res Commun; 106(3):947-952 1982

Injection of 5 mg of single stranded polyriboinosinic acid/kg body wt into male Swiss Random mice followed 1 hr later by injection of 5 mg of single stranded polyribocytidylic acid/kg resulted in losses of ethylmorphine N-demethylase activity and cytochrome P-450 similar to those elicited by 10 mg/kg of double stranded polyriboinosinic.polyribocytidylic acid. Large serum interferon levels were observed after administration of the single-stranded compounds in the same order. When the order was reversed, neither of these effects were observed. (19 Refs)

23. EFFECT OF 7,12-DIMETHYLBENZ[A]ANTHRACENE ON PRODUCTION AND ACTION OF GAMMA INTERFERON.

Golemboski KA, DeLor DK, Streips UN, Sonnenfeld G

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JNCI; 68(6):993-996 1982

Spleens were removed from Swiss Webster mice, and cultures of spleen cells were prepared. Gamma interferon (Type II immune) production was induced in these cells by addition of the purified protein form of phytohemagglutinin (PHA-P) to the cultures. When 7,12-dimethylbenz[a]anthracene was added to the cultures either before or after addition of PHA-P, the production of gamma IFN was inhibited. The degree of inhibition was greater when the cells were treated with DMBA before addition of PHA-P. In experiments to determine the effects of DMBA on the antivirus activity of previously prepared gamma IFN preparations, DMBA was either added to target cells before the addition of exogenous gamma IFN or mixed together with exogenous gamma IFN. In both cases, the antivirus activity of this exogenous gamma IFN was not affected. These data suggest that DMBA treatment can inhibit the production but not the antivirus activity of murine gamma IFN. (Author abstract) (13 Refs)

24. INTERFERON INDUCTION IN HEALTHY AND TUMOR-BEARING DOGS BY CELL WALLS OF MYCOBACTERIUM BOVIS STRAIN BACILLE CALMETTE-GUERIN.

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Am J Vet Res; 43(7):1232-1237 1982

High titers of interferon (IF) were released into the circulation of 8 of 10 adult, female, healthy dogs (Group A) and 7 of 10 pet dogs (Group C) bearing naturally occurring primary malignant mammary tumors after they were given a single dose (4 mg/ml) of a Mycobacterium bovis bacille Calmette-Guerin cell wall (BCG-CW) emulsion. This BCG-CW emulsion had been administered into one mammary gland in the 10 healthy dogs and intratumorally in the 10 dogs bearing biopsy-confirmed malignant mammary tumors. Increases in IF titers were not detected in sera from 10 dogs (Group D) bearing malignant mammary tumors injected with placebo, from 10 dogs (Group E) after surgical excision of malignant mammary tumors, and from 15 noninjected healthy control dogs (group B). The IF detected in the sera of tumor-bearing and healthy dogs following injection of BCG-CW was effective against vesicular stomatitis virus and influenza A virus when tested in Madin-Darby canine kidney cells, but not in human KB cells. Vesicular stomatitis viral antibody was not detected by neutralization tests nor radioimmunoassays in sera from the subjects. At entry into the study of 30 dogs with malignant mammary tumors (Groups C, D, and E) and of 25 healthy dogs (Groups A and B), titers of IF were detected in 14 of the former and in 1 of the healthy dogs. There was no correlation between the pretreatment IF titers in tumor-bearing dogs and age, clinical history, breed, previous pregnancies, or tumor vol. In tumor-bearing dogs injected with BCG-CW (Group C), there was no apparent relationship between the induction of high titers of IF and any previously mentioned factors, the amount of BCG-CW injected, or serum levels of antibody specifically reactive with BCG-CW or canine viral antigens. (Author abstract) (37 Refs)

INTACT MICROBIAL ORGANISMS IN IMMUNOTHERAPY

25. STUDIES OF MONOCYTOPOIESIS IN PATIENTS WITH MALIGNANT DISEASE AND AFTER IMMUNOSTIMULATION WITH BCG, USING 3H-THYMIDINE AS A DNA LABEL.

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Nuklearmedizin; 21(2):49-52,53-54 1982

Proliferation of monocytes was studied in 69 patients with malignant diseases. Patients included 8 with Hodgkin's disease (HD), 15 with non-Hodgkin's lymphoma (NHL), 9 with mycosis fungoides (MF), 10 with breast cancer (BC), and 27 with malignant melanoma (MM). Monocytic proliferation was measured in all patients prior to treatment. 3H-Thymidine was used as a DNA label. Monocytic proliferation was also measured in eight patients with BC and 8 with MM after two and four immunostimulations with BCG and in 27 patients with MM at 4-wk intervals before BCG immunostimulation for a period of up to 10 mo. Patients with each type of malignancy showed increased proliferation before treatment. All patients with HD showed increases in the fraction of monocytes in the bone marrow (BMM: 6.4%, compared with 2.8% in normal individuals), thymidine labeling index (TLI: 20.0 vs 12.1), and fraction of peripheral blood monocytes (PBM: 617 vs 325). Among 15 patients with NHL, BMM was 3.3%; TLI in the bone marrow was below normal in 6 patients, normal in 5, and above normal in 3. In patients with MF, BMM was 4.8%, TLI 32.0, and PBM 738. In patients with MM, BMM was 3.7%, TLI 14.9, and PBM 398. In patients with BC, BMM was 4.6%, TLI 12.0, and PBM 569. Postoperative prophylactic BCG stimulation increased the proliferation of monocytes. Proliferation returned to normal, however, 4-6 mo after the start of BCG therapy. Monocytopoiesis is evidently stimulated by malignancies. BCG increases monocytopoiesis only during mo 1 of therapy. (22 Refs) (In GER)

26. IMMUNOTHERAPY OF METASTASES ENHANCES SUBSEQUENT CHEMOTHERAPY.

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Science; 217(4557):367-369 1982

In many multimodal therapies of cancer, postsurgical chemotherapy is administered before immunotherapy for treatment of micrometastatic disease. This sequence may not be the most efficacious. Experiments in which Strain 2 guinea pigs bearing syngeneic L10 hepatocarcinomas were given immunotherapy showed that infiltrating immune effector cells not only were tumoricidal but disrupted the characteristically compact structure of metastatic foci. When cytotoxic drugs were administered at the peak of this inflammatory response, the survival rate of the guinea pigs increased significantly. We conclude that postsurgical immunotherapy can enhance the effect of cytotoxic drugs administered subsequently. (Author abstract) (18 Refs)

MICROBIAL FRACTIONS AND EXTRACTS

27. INHIBITION OF RAT ADENOCARCINOMA METASTASES BY 'STAPHYLOCOCCUS AUREUS' PROTEIN A.

Cowan FM, Klein DL, Armstrong GR, Ablashi DV, Pearson JW, Bensinger WI
Pharmacia AB, Box 181, S-75104 Uppsala 1, Sweden
Biomedicine; 36(1):29-31 1982

Fischer F344/CRBL female rats were injected intravenously with 10(6) syngeneic 13,762 adenocarcinoma cells, and daily doses of either 10 ug, 100 ug or 1 mg Staphylococcus aureus protein A were administered intraperitoneally on Days 1 through 11. The animals were sacrificed on Day 12, their lungs infused with Bouin's solution, and lung metastases counted. A significant reduction in the number of visible metastatic nodules was observed in the animals given 100 ug and 1 mg of Staphylococcus aureus protein A daily. (Author abstract) (33 Refs)

28. PREVENTION AND THERAPY OF L1210 LEUKEMIA IN MICE, USING INACTIVATED AND GRAFTED TUMOR CELLS, IN ASSOCIATION WITH THE IMMUNOMODULATOR P40, AND ANTINEOPLASTIC AGENTS.

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C R Seances Acad Sci [III]; 294(12):571-576 1982

The effect on L1210 leukemia in mice of immunostimulation with P40 fraction isolated from C granulosum and inactivated L1210 cells coupled with tetanus toxoid, in combination with various therapies including or excluding chemotherapy, daunorubicin or mitomycin is reported. The results of immunostimulating treatments were inconclusive. However, when chemotherapy was preceded and followed with immunostimulation, the results were much more promising. In particular the association of nonspecific immunotherapy with P40 and with a specific immunotherapy with inactivated L1210 cells had strong inhibiting effects on the tumor development. The treatment of L1210 cells in vitro with antitumoral agents in weak concentrations reduced their pathogenicity. The use of these treated cells resulted in the induction of a strong resistance to tumor development without any complementary chemotherapy. (6 Refs) (In FRE)

CYTOKINE THERAPY

29. PRODUCTION OF MACROPHAGE-ACTIVATING FACTOR BY T LYMPHOCYTE CLONES AND CORRELATION WITH OTHER LYMPHOKINE ACTIVITIES.

Kelso A, Glasebrook AL, Kanagawa O, Brunner KT
Dept. Immunology, Swiss Inst. Experimental Cancer Res., 1066 Epalinges, Switzerland
J Immunol; 129(2):550-556 1982

The production of macrophage-activating factor (MAF) by antigen-stimulated murine T lymphocyte clones has been compared with their cytolytic function and release of other lymphokines. MAF activity was measured by the capacity of peptone-induced peritoneal exudate cells or bone marrow-derived macrophages to lyse 51Cr-labeled tumor cells after incubation with supernatant from the stimulated T cells and a nonactivating, amplifying dose of lipopolysaccharide. Of 72 clones generated against H-2, Mls, H-Y, or Moloney leukemia virus-associated antigens, 68 were found to produce detectable quantities of MAF. Release of MAF by clones (1) occurred within 1 to 12 hr of exposure to antigen, (2) required stimulation with cells of the relevant antigenic specificity, and (3) could also be induced by concanavalin A, indicating that the cloned cells were the source of the activity. The capacity of a clone to produce MAF was independent of its antigenic specificity, cytolytic activity, or ability to produce interleukin 2 or granulocyte-macrophage colony-stimulating activity. In contrast, production of interferon and MAF was not dissociated for any of the clones tested. (Author abstract) (42 Refs)

30. INHIBITION OF CYTOKINE PRODUCTION BY A TUMOUR CELL PRODUCT.

Farram E, Nelson M, Nelson DS, Moon DK
(c/o Nelson, D. S.) Kolling Inst. Medical Res., Royal North Shore Hosp., St. Leonards, NSW 2065, Australia
Immunology; 46(3):603-612 1982

Supernatants from cultured mouse and human tumor cells, but not mouse or guinea-pig fibroblasts, inhibited the production of a lymphokine, macrophage chemotactic factor, by PHA-stimulated mouse spleen cells. The supernatants affected spleen cells from old, but not young, mice. They were most active if added at the start of the spleen cell culture and did not act by binding phytohemagglutinin (PHA). The active material had an approx mol wt, on membrane filtration, of 1,000-10,000 and could be bound to and eluted from Con A-Sepharose. Tumor supernatant factor(s) of similar mol wt inhibited the production of interleukin 1 (lymphocyte activating factor) in response to lipopolysaccharide by stimulated thioglycollate-induced peritoneal exudate macrophages, but not by Corynebacterium parvum-activated macrophages. Similar tumor-produced material has been found to inhibit the early phase of delayed-type hypersensitivity reactions in older mice. It is suggested that this effect is due, at least in part, to inhibition of interleukin 1 production leading to inhibition of lymphokine production. (Author abstract) (26 Refs)

THYMIC HORMONES AND OTHER IMMUNORESTORATIVE AGENTS

31. DECREASE OF TUMOR GROWTH IN MICE AFTER INTRAVENOUS THYMOSIN-TREATED BONE MARROW CELL INJECTION.

Cupissol D, Rey A, Goldstein AL, Serrou B
Laboratoire d'Immunopharmacologie des Tumeurs, INSERM U 236, ERA-CNRS No. 844, Centre Paul Lamarque, Hopital Saint-Eloi, B P 5054, 34033 Montpellier Cedex, France
JNCI; 69(1):27-31 1982

The effect of iv injection in C57BL/6 mice of 3 x 10(7) bone marrow cells preincubated in either thymosin fraction V or thymosin alpha-1 was evaluated on the growth of a 3-methylcholanthrene-induced transplantable tumor in a syngeneic system. The effect was then compared to that elicited by theophylline or levamisole, which both demonstrated thymosin-like action in vitro. The results showed significantly retarded tumor growth (P less than 0.001) and prolonged survival time (P less than 0.001) when thymosin fraction V was used. The same results were obtained with thymosin alpha-1 with use of the same protocol but only one-twentieth of the concentration of fraction V. Theophyline and levamisole demonstrated no antitumor effect. (Author abstract) (42 Refs)

ACTIVE SPECIFIC IMMUNIZATION

32. SPECIFIC TUMOR IMMUNITY PRODUCED BY THE INJECTION OF VACCINIA VIRAL ONCOLYSATES.

Walleck MK
Dept. Surgery, Washington Univ. Sch. Medicine, St. Louis, MO, 63110
J Surg Res; 33(1):11-16 1982

A live vaccinia vaccine virus-augmented and lysed tumor cell vaccine (vaccinia oncolysate) is used as a specific active immune mechanism stimulator in a syngeneic SV40-transformed BALB/c male mouse peritoneal macrophage tumor system. BALB/c mice pretreated with sc injections of vaccinia oncolysates prior to challenge with tumor cells failed to develop tumors at the injection sites. Cross-immunization and immunotherapy experiments were also performed. Because of the encouraging results in this murine tumor system, preliminary trials were instituted to evaluate vaccinia oncolysates as an immunotherapeutic agent in human cancer. (Author abstract) (15 Refs)

33. PRODUCTION OF A TUMOR-SPECIFIC XENOANTISERUM FROM PARTIALLY PURIFIED IMMUNOPROTECTIVE TUMOR ANTIGEN.

Tanaka T, Yamagishi H, Pellis NR, Kahan BD
(c/o Pellis) Dept. Surgery, Div. Organ Transplantation, Univ. Texas Medical Sch. at Houston, Houston, TX, 77030
Cancer Immunol Immunother; 13(1):48-52 1982

Raising of specific xenoantisera in rabbits by purified tumor-specific transplantation antigens (TSTA) preparations was studied. Serum from the rabbit immunized with partially purified 3-methylcholanthrene (MCA)-F tumor TSTA (fraction 15, Fr 15) displayed a complete or semi-circular ring reaction in the immunofluorescence assay at a titer of 1:4 when a fluorescein isothiocyanate-conjugated goat anti-rabbit IgG serum was used at a dilution of 1:8. Absorption with 10(8) intact MCA-F cells diminished the ability of 1 ml anti-Fr 15 serum to bind MCA-F cells by 95%. On the other hand, absorption with MCA-D or MCA-T cells did not significantly inhibit the immunofluorescence reaction. Preincubation with 30 mg 3 M KCl extract or with 7.5 mg Fr 15 completely inhibited the binding capacity of 1 ml anti-Fr 15 serum. No significant difference in the fluorescence between cells stained after 5-hr incubation at 37 C and cells stained immediately was observed. Thus neither macrophages nor other Fc receptor-bearing cells significantly contributed to the proportion of tumor-derived cells exhibiting fluorescence. The xenoantibody displayed specific immunologic reactivity in the indirect membrane immunofluorescence assay, suggesting that administration of purified materials may afford new reagents with which to dissect and purify TSTA. (23 Refs)

ADOPTIVE IMMUNIZATION AND RELATED APPROACHES

34. ADOPTIVE CHEMOIMMUNOTHERAPY OF A SYNGENEIC MURINE LYMPHOMA WITH LONG-TERM LYMPHOID CELL LINES EXPANDED IN T CELL GROWTH FACTOR.

Eberlein TJ, Rosenstein M, Spiess P, Wesley R, Rosenberg SA
Surgery Branch; Div. Cancer Treatment, NCI, NIH, Bethesda, MD, 20205
Cancer Immunol Immunother; 13(1):5-13 1982

The cure of disseminated syngeneic FBL-3 lymphoma in female C57/BL/6 mice was attempted with the use of in vivo-immunized cells, in vitro-sensitized cells, whole lymphoid populations expanded in T cell growth factor (TCGF), and with cloned cytotoxic cells expanded in TCGF. In 3/3 experiments, 20/38 mice receiving cytoxan (CY) plus in vivo-immunized lymphoid cells were cured of tumor compared to 0/31 mice treated with CY plus normal lymphocytes. In vivo-immunized lymphocytes were resensitized to irradiated FBL-3 tumor in complete medium (CM) or lectin-free TCGF (LF-TCGF). In the CM group 41/50 animals were cured. In the LF-TCGF group 36/61 animals were cured. No significant difference was observed in the in vivo effects of cells in vitro sensitized (IVS) in CM or LF-TCGF. IVS cells were resensitized in vitro to irradiated FBL-3 tumor for 5 days. Simultaneously, normal C57BL/6 lymphocytes were co-cultured with normal C57BL/6 irradiated stimulators. Neither of these groups showed significant lysis of fresh FBL-3 tumor in an 18-hr 51Cr-release assay in six of eight experiments. Treatment of mice with CY plus immune lymphocytes sensitized to normal C57BL/6 stimulators and then expanded in LF-TCGF resulted in no increase in survival compared with CY alone. Treatment of mice with CY plus immune lymphocytes resensitized to FBL-3 tumor in vitro and expanded in LF-TCGF cured 7/27 animals and prolonged survival over that in all control groups. Treatment with CY plus normal nonimmune lymphocytes resensitized to normal C57BL/6 stimulators and expanded in LF-TCGF for 2.5 mo did not prolong survival compared with CY controls. CY plus immune lymphocytes sensitized to FBL-3 tumor and expanded continuously in LF-TCGF for 2.5 mo showed marked prolongation of survival and cured 5/9 mice. Implications of results for application of these techniques to other less antigenic tumors and human cancers are discussed. (49 Refs)

SEROTHERAPY AND RELATED APPROACHES

35. REGRESSION OF CANINE MAMMARY CARCINOMA AFTER IMMUNOADSORPTION THERAPY.

Holohan TV, Phillips TM, Bowles C, Deisseroth A
(c/o Bowles) Hazelton Lab America, Inc., 9200 Leesburg Pike, Vienna, VA, 22180
Cancer Res; 42(9):3663-3668 1982

The plasma of dogs afflicted with mammary carcinoma was perfused through chambers bearing Staphylococcus aureus Cowan Strain 1 in an attempt to remove tumor-promoting, immunosuppressive immune complexes from the peripheral blood of these animals. In this canine model of spontaneous mammary carcinoma, reduction of breast and/or soft-tissue tumor (posttreatment size equal to 0 to 50% of pretreatment tumor size) was observed in 5 of the 10 animals so treated. Immune complexes capable of blocking lymphocytotoxicity were measured pre- and postimmunoadsorption; removal was more efficient in the five responders (4 of 6 complexes) than in nonresponders (1 of 10 complexes), although statistical significance was not attained. The reduction of tumor size seen in soft-tissue sites was not always accompanied by a similar reduction of tumor size in visceral sites, and surgical resection of residual soft-tissue tumor nodules remaining after immunoadsorption treatment was required to achieve a complete response in two responding animals. No significant decrease in tumor size was observed in the control group, perfused without immunoadsorbent, nor in five additional tumor-bearing animals infused with normal dog plasma which had been passed through S aureus Cowan Strain 1-containing chambers. These data indicate that immunoadsorption of tumor-bearing host plasma can result in reduction in size of canine mammary adenocarcinoma but that the response is dependent on the site of the tumor (sc versus visceral) and may require utilization of other modalities to achieve a complete disappearance of the tumor. (Author abstract) (31 Refs)

36. CLINICAL STUDIES OF ADENOCARCINOMA WITH MONOCLONAL ANTIBODIES TO PANCREATIC TUMOR ANTIGENS (MEETING ABSTRACT).

Metzgar RS, Daasch VN, Gaillard MT, Fernsten PD, Borowitz MJ
Department of Microbiology, Duke University Medical Center, Durham, NC, 27710
Hybridoma; 1(2):182 1982

We have elicited and characterized 5 murine monoclonal antibodies (DU-PAN-1,2,3,4 and 5) to a human pancreatic tumor cell line, HPAF. An immunoperoxidase technique was used to determine the presence of the antigens in frozen sections of various tumors, and adult and fetal normal tissues. DU-PAN-1 antigen has so far been detected only on pancreatic tumors and a transitional cell carcinoma of the bladder. DU-PAN-2 antigen was present on pancreatic ductal epithelial cells and on tumor cells from many other adenocarcinoma patients. DU-PAN-3 antigen was present on adult and fetal pancreatic cells and certain tumor cells but could not be detected on cells of other fetal or adult normal tissues. DU-PAN-4 and 5 antigens have a more widespread distribution on normal or tumor cell types. Radioimmune precipitation studies have established the molecular properties of all antigens except DU-PAN-4. Strong inhibitory activity (greater than 80%) often at a titer greater than 50 was noted with ascitic fluid from pancreatic and ovarian cancer patients. Serum from most patients with pancreatic tumors as well as some patients with ovarian, breast, and colon, adenocarcinomas demonstrated significant inhibitory activity. Serum and ascites from patients with non-malignant disease demonstrated little or no blocking activity. No inhibition was noted with purified CEA (carcinoembryonic antigen), sialic acid or blood group antigens. Antigen levels from serial testing of sera of pancreatic and ovarian cancer patients correlated well with their clinical status. (no Refs)

37. MONOCLONAL ANTIBODY SEROTHERAPY OF SOLID TUMORS: A GUINEA PIG MODEL I. CHARACTERIZATION OF MONOCLONAL ANTIBODY (MEETING ABSTRACT).

Bernhard MI, Foon KA, Clarke GC, Christensen WL, Hoyer L, Key M, Hanna MG, Oldham RK
National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD, 21701
Hybridoma; 1(2):204 1982

We have chosen the chemically induced, transplantable L10 hepatocellular carcinoma of strain 2 guinea pigs as a model system to study monoclonal (MoAb) immunotherapy of cancer for several compelling reasons: (1) This model provides a transplantable syngeneic solid tumor with metastatic potential similar to solid tumors in man; (2) Immune responses in the guinea pig are somewhat analogous to those of man; (3) Guinea pigs are exquisitely sensitive to anaphylactic shock, a consideration in cancer immunotherapy utilizing murine antibodies; and (4) The guinea pig model should have utility for coupling radionuclides for imaging studies and coupling of toxins and drugs to MoAb for therapy trials. Monoclonal antibodies were prepared to the L10 tumor and an IgG1 producing clone (D3) was selected for further study. Two dimensional gel electrophoresis confirmed the monoclonality of the D3 antibody. Radioimmunoassays and membrane fluorescence (FACS IV) revealed no cross reactivity with normal tissues or the similarly derived L1 tumor. Immunoperoxidase assays performed on cryostat sections of tumor metastases and normal tissues also showed specific L10 tumor reactivity. Radioimmunoprecipitation of detergent extracts of L10 cells demonstrated the antigen on a polymeric molecule of 148,000 dalton unit size. Serotherapy trials using repeated intravenous injections at widely varying dosages have produced significant reduction in tumor size without demonstrable side effects until the fourth treatment. Immunoperoxidase studies following monoclonal antibody infusion have shown specific localization of monoclonal antibody on primary and metastatic tumor. (no Refs)

38. THE USE OF MONOCLONAL ANTIBODIES IN THE DIAGNOSIS OF GASTROINTESTINAL TUMORS (MEETING ABSTRACT).

Herlyn M, Koprowski H
The Wistar Institute of Anatomy and Biology, 36th Street at Spruce, Philadelphia, PA, 19104
Hybridoma; 1(2):205 1982

Attempts have been made to use monoclonal anti-colorectal carcinoma antibodies as tools in the diagnosis of gastrointestinal tumors. The first approach is based on the detection of tumor-associated antigens in the serum of patients with gastrointestinal tumors. A radioimmunoassay has been developed in which the inhibition of binding of monoclonal antibodies to target preparations by specific antigen in human serum is determined. Binding inhibition of one anti-colorectal carcinoma antibody was shown by 163 of 255 (64%) sera from patients with various stages by carcinoma of colon and rectum, by 45 of 49 (95%) sera from patients with pancreatic carcinoma, and by 8 of 11 (73%) sera from patients with gastric carcinoma. By contrast, 7 of 89 (8%) sera from patients with other malignancies, 9 of 68 (15%) sera from patients with inflammatory bowel diseases and polyposis, and 2 of 108 (2%) sera from healthy donors inhibited binding of monclonal antibody. The second diagnostic approach is based on the binding of monoclonal antibodies to fixed, paraffin-embedded tumor sections, using a four-step immunoperoxidase technique. The antibodies bind to tissue sections of carcinoma of colon, rectum, stomach and pancreas but not to normal gastrointestinal mucosa or to normal pancreatic acini. Only pancreatic duct cells and bronchial glands express the antigen binding these antibodies. As a third approach in the diagnosis of gastrointestinal tumors, preliminary experiments have been done to localize human colon carcinoma tumors grown in athymic nude mice using radiolabeled anti-tumor antibodies. (no Refs)

39. SERUM ANTIGEN TUMOR MARKER FOR COLON CARCINOMA: (MEETING ABSTRACT).

Sears HF, Koprowski H, Herlyn M, DelVillano B, Steplewski Z
The Wistar Institute, Philadelphia, PA, 19104
Hybridoma; 1(2):217 1982

We have shown that a monoclonal anticolorectal cancer (CRC) antibody can identify a tumor associated antigen in the sera of 70% of patients with advanced CRC. We used two monoclonal antibodies which bind to monosialogangliosides on the surface of CRC cells to identify these tumor associated glycolipids in the serum of 85 patients with primary CRC tumors. The results were compared to these patients' stage of disease and their CEA (carcinoembryonic antigen) levels. We studied longitudinally collected sera of these patients at high risk for recurrence. We were able to test all the sera from one patient at one time because of the stability of the antigen. Sixty-six of 85 patients had at least one antigen elevation in the perioperative period, 39 detected by antibody 52A binding inhibition, 42 detected by direct RIA (radioimmunoassay) using antibody 19-9, and 37 by CEA. Levels were not related to Dukes' stage (A-C). The presence of one antigen did not predict the presence or absence of another antigen. Six antigens were not detected preoperatively in patients in whom the antigen was detected in the follow-up period prior to detection of clinical recurrence. The decay of antigen level by 7 days after the removal of the primary tumor was erratic and not predictive of recurrence. Twelve of the 35 patients with B2 or C stage primary tumor have had a recurrence. Sera for serial assays was obtained every 3 months. Antigen elevations in these longitudinally collected sera predicted the recurrences by at least 3 months to as much as 18 months prior to clinical discovery in 10 of the 12 patients. In 7 patients, one of the monoclonal-antibody identified-antigens never returned to normal, and in 3 patients antigen levels fell only to rise again many months prior to clinical recognition of recurrence. (no Refs)

40. THE IMMUNOHISTOCHEMICAL REACTIVITY OF A HUMAN MONOCLONAL ANTIBODY WITH TISSUE SECTIONS OF HUMAN MAMMARY TUMORS.

Teramoto YA, Mariani R, Wunderlich D, Schlom J
(c/o Schlom) Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205
Cancer; 50(2):241-249 1982

Human monoclonal antibodies have been generated following the fusion of human lymphocytes (obtained from axillary lymph nodes of mastectomy patients) with a murine nonimmunoglobulin secreting myeloma cell line. We report a detailed analysis of the reactivity of a human IgM monoclonal antibody secreted by one of these double cloned hybridoma cell lines. Tissue sections of both malignant and benign human mammary tumors, as well as apparently normal tissues, were tested using the immunoperoxidase technique and the human monoclonal antibody. Eighty-one per cent (54/67) of primary malignant mammary tumors, 100% (20/20) of metastatic breast lesions, and 14% (3/22) of benign breast lesions reacted positively with a moderate or strong intensity. The per cent of mammary carcinoma cells that stained and the pattern of staining varied among different tumor samples. While reactivity was observed with selected carcinomas of nonbreast origin, little or no reactivity was observed with apparently normal human tissues including normal mammary epithelium. The antibody reactivity observed was shown to be clearly distinct from those of both anti-T and anticarcinoembryonic antigen sera. (Author abstract) (19 Refs)

41. PHENOTYPE OF CELLS INVOLVED IN MYCOSIS FUNGOIDES AND SEZARY SYNDROME (BLOOD AND SKIN LESIONS): IMMUNOMORPHOLOGICAL STUDY WITH MONOCLONAL ANTIBODIES.

Schmitt D, Souteyrand P, Brochier J, Czernielewski J, Thivolet J
Dept. Dermatology, Hopital Edouard-Herriot, F-69374 Lyon Cedex 2, France
Acta Derm Venereol (Stockh); 62(3):193-199 1982

The phenotypic expression of immunocompetent cells involved in lesions of cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome) was studied by using monoclonal antibodies specific for T-cell subsets and HLA-DR antigens (OKT3, T4, T6, T8) (BL 6, BL 5, BL 2). In Sezary syndrome, the phenotype of Sezary cell is homogeneous (T3+, T4+, T8-, T6-, BL2-) and corresponds to the phenotype expressed by the normal helper T-cell population. At the ultrastructural level, the discontinuous distribution of OKT4 and OKT3 antigenic sites on the cell surface is similar to the HTLA antigens. In skin lesions, the Langerhans cells expressed two specificities shared by normal thymocytes (T6 and BL6). We suggest that the expression of these antigens could be related to the epithelial microenvironment (epithelium-dependent differentiation antigens). The tumoral lymphoid cells infiltrating the skin showed the same phenotype (helper type) as the circulating Sezary cells (T3+, T4+, T8-, T6-). Moreover, The T3+ cells also expressed HLA-DR antigens and corresponded to activated T lymphocytes. The various subpopulations of immunocompetent cells seemed to be related to the MHC-derived antigens. (Author abstract) (29 Refs)

OTHER BIOLOGICAL RESPONSE MODIFIERS

42. RETINOIC ACID SUPPRESSION OF HUMAN LEUKOCYTE INTERFERON PRODUCTION.

Abb J, Abb H, Deinhardt F
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Immunopharmacology; 4(4):303-310 1982

The effect of retinoic acid (RA) on the production of interferon (IFN) by human peripheral blood leukocytes was investigated in vitro. Concomitant administration of RA and viral or nonviral IFN inducers to WBC cultures suppressed the production of IFN in a dose-dependent fashion. Max suppression of IFN yields were observed at an RA concentration of 15 ug/ml. A similar reduction in IFN yields was observed with RA added to sendai virus- or influenza virus-stimulated human lymphoblastoid cells. Incubation of WBC or lymphoblastoid cell lines (LCL) in the presence of 0.15% dimethylsulfoxide and IFN inducers had no significant effect on the basic production of antiviral activity. The inhibitory effect of RA on leukocyte IFN production in response to purified phytohemagglutinin (PHA-P) or influenza virus depended upon its near-concurrent addition to the cultures. Antiviral activity induced by treatment with PHA-P or concanavalin A was characterized as IFN-gamma. That induced by treatment with Corynebacterium parvum, viruses, polyinosinic-polycytidilic acid, or tumor cell lines shared properties with IFN-alpha. Addition of RA to WBC cultures markedly suppressed IFN yields in supernatants of human WBC incubated with lectin mitogens, bacterial products, viruses, polynucleotides, and lymphoblastoid tumor cells. The degree of suppression of IFN secretion by RA was similar with inducers of IFN-gamma and IFN-alpha. Implications of these findings for the use of retinoids for treatment of human cancer are discussed. (24 Refs)

CLINICAL IMMUNOLOGY

43. EFFECTS OF DIPHENYLHYDANTOIN ON KILLER CELL ACTIVITY AND OTHER IMMUNOLOGICAL FUNCTIONS. A SEQUENTIAL STUDY INCLUDING THE INTERACTION OF CORYNEBACTERIUM PARVUM IN MELANOMA PATIENTS.

Thatcher N, Wan HH, Swindell R, Wilkinson PM, Crowther D
Dept. Medical Oncology, Christie Hosp. and Holt Radium Inst., Wilmslow Road, Manchester M20 9BX, England
Int J Immunopharmacol; 4(3):167-174 1982

The effects of a single dose of phenytoin (PHEN; 300 mg/square meter) upon killer cell (NK) cytotoxicity, serum immunoglobulins, and T and B cell proportions was investigated prospectively in 11 patients (6 males, 5 females) with metastatic malignant melanoma. No acute change in T lymphocyte rosettes, serum immunoglobulins, and DNA synthesis of lymphocyte cultures were observed after PHEN treatment. An early immunosuppression occurred within 10 hr after PHEN with reductions in lymphocyte count and NK activity. This suppression was reversible, with apparent recovery by 58 hr. Such a feature could explain the transient lymphadenopathy observed before cessation of PHEN medication. The profound and early immunosuppression associated with the first PHEN dose was abrogated by Corynebacterium parvum immunization (iv infusion 2 mg/square meter in 300 ml physiological saline over 3 hr) preceding a second dose of PHEN. While the second dose of PHEN caused some immunosuppression, no increase in T cells, NK, and phytohemagglutinin induced cytotoxicity above initial values was observed. (23 Refs)

44. CIRCULATING IMMUNE COMPLEXES DETECTED BY BINDING OF RADIOLABELLED PROTEIN A IN PATIENTS WITH ORAL CANCER AND ORAL PREMALIGNANT LESIONS.

Scully C, Barkas T, Boyle P, McGregor IA
Dept. Oral Medicine and Pathology, Glasgow Dental Hosp. and Sch., Glasgow Univ., 378 Sauchiehall St., Glasgow G2 3JZ, Scotland
J Clin Lab Immunol; 8(2):113-115 1982

Serum immune complexes and immunoglobulins were examined in 48 Caucasian patients with histologically confirmed squamous cell carcinoma, 17 with oral keratosis and variable degrees of epithelial dysplasia (leukoplakia), and 49 controls matched as closely as possible for age and sex. Circulating levels of immune complexes (expressed as ug equivalents aggregated IgG/ml) were significantly higher in patients with oral cancer, median 33, than in controls, 13, but not significantly higher than in patients with oral keratosis, 22. No correlation could be determined between serum levels of immune complexes and the clinical stage in patients with oral cancer. (30 Refs)

45. SUPPRESSOR CELL ACTIVITY IN PERIPHERAL BLOOD OF PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE TONSIL.

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Ear, Nose, Throat Clinics, Ludwig-Maximillians-Universitat, Munich, W. Germany

Excerpta Med Int Congr Ser; 582:249-253 1982

The suppressive activity of mononuclear cells in 62 patients with squamous cell carcinoma of the tonsil was investigated. Patients were treated with surgery plus irradiation, irradiation alone, or irradiation plus chemotherapy. Two tests were used as indicator systems: the phytohemagglutinin stimulated culture, and the one-way mixed lymphocyte reaction. Suppressor activity (SA) of peripheral blood lymphocytes of healthy controls was approx 20%. SA was similar in patients treated by surgery prior to surgery and increased after surgery. Similar findings were reported after irradiation. However, after chemotherapy, SA fell from approx 40% to approx 10%, reflecting the immunosuppressive activity of the chemotherapy. Total SA of activated and spontaneous suppressor cells fluctuated around normal values. SA was low in patients showing no signs of disease and high in patients with growing tumors. SA was high in patients with inoperable disease, decreased and fluctuated over the next 12 mo, then reached a max at 14 mo. SA in lymph nodes was always higher than that in peripheral blood. Lymph node lymphocytes showed a marked increase in SA when tested in allogenic blast formation, suggesting a direct effect of the tumor on suppressor cell population. No correlation of SA with tumor stage could be found. (no Refs)

46. THE IN VIVO EFFECT OF A THYMIC FACTOR (THYMOSTIMULIN) ON IMMUNOLOGIC PARAMETERS OF PATIENTS WITH UNTREATED HODGKIN'S DISEASE.

Martelli MF, Velardi A, Rambotti P, Cernetti C, Bertotto A, Spinozzi F, Bracaglia AM, Falini B, Davis S

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Cancer; 50(3):490-497 1982

The in vivo effect of a calf thymus extract (thymostimulin, TS) on the E-rosetting capacity. PHA blastogenic response, serum migration inhibitory activity (LIF) and skin reactivity to recall antigens was evaluated in 19 untreated patients with Hodgkin's disease. In patients the mean percentage of peripheral blood lymphocytes forming E-rosettes increased from 47 to 55.7% (p less than or equal to 0.001; normal: 58.9). The mean PHA stimulation index rose with all three concentrations tested but did not reach normal values. Serum LIF was positive in only one patient prior to treatment with a total patient mean LIF of 1.03. Nine patients developed a positive LIF following treatment with a mean LIF for all patients of 0.75 (p less than or equal to 0.005). Skin tests were positive in 10 patients (52.6%) prior to therapy and 18 patients following therapy (94.7%; p less than or equal to 0.05). Thymostimulin, in vivo, appears to return immunologic competency to a population of untreated patients with Hodgkin's disease. (Author abstract) (74 Refs)

47. AUGMENTATION OF NATURAL KILLER CELL ACTIVITY AFTER ARTERIAL EMBOLIZATION OF RENAL CARCINOMAS.

Bakke A, Gothlin JH, Haukaas SA, Kalland T
Dept. Anatomy, Univ. Lund, Biskopsgaten 7, S-223 62 Lund, Sweden
Cancer Res; 42(9):3880-3883 1982

Preoperative embolization of the renal artery has been reported to improve the survival of patients with advanced renal carcinomas compared to operative treatment only. To investigate possible immunological consequences of tumor embolization, natural killer (NK) cell activity in peripheral blood was investigated immediately before and at different time intervals after occlusion of the renal artery by insertion of a metal coil. A slight increase in NK activity could be observed 24 hr postembolization while a marked augmentation was seen after 48 hr. The high NK activity persisted up to 96 hr after embolization, the last time period included in the study. Two patients undergoing the same procedure but in whom embolization was unsuccessful showed no alteration in NK activity. It is suggested that interferon produced by macrophages activated by the necrotizing tumor might be responsible for the augmentation of NK activity. (Author abstract) (31 Refs)

48. THE IMMUNOLOGICAL CLASSIFICATION OF LEUKAEMIA BASED ON A RAPID MICROCYTOTOXICITY TEST.

Billing RJ, Foon KA, Linker-Israeli M
1000 Veteran Ave., Los Angeles, CA, 90024
Clin Exp Immunol; 49(1):142-148 1982

We describe a rapid, accurate, and reproducible cytotoxic antibody test for the immunological classification of leukemia. Well characterized heteroantisera and monoclonal antibodies were distributed in a microcytotoxicity tray referred to as a leukemia screening tray (LST). Leukemia cells were tested for the presence of Ia-like, 'blast', thymocyte, common acute lymphoblastic leukemia (cALL), and acute myeloblastic leukemia (AML) antigens. Utilizing this technique, T ALL could be distinguished from non-T ALL, ALL and AML could be differentiated, the myeloid blast crisis of chronic myelogenous leukemia (CML) could be distinguished from the lymphoid blast crisis, and the T lymphocyte and B lymphocyte lymphoid leukemias were readily identified. It has been shown that subclassification of leukemia according to surface markers, as described here, offers considerable improvement in the diagnosis and treatment of leukemia over the classical morphological methodologies. Because the test can be completed in 2 hr and unlimited amounts of monoclonal antibodies are available, the LST or similar tests should become universally available in the future to supplement morphological data and replace other lengthy enzyme and rosetting tests. (Author abstract) (34 Refs)

49. IMBALANCE OF T CELL SUBPOPULATIONS IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA OF THE B CELL TYPE.

Herrmann F, Lochner A, Philippen H, Jauer B, Ruhl H
Dept. Hematology and Oncology, Klinikum Steglitz, Free Univ. Berlin, Hindenburgdamm 30, D-1000 Berlin 45, W. Germany
Clin Exp Immunol; 49(1):157-162 1982

T cell enriched mononuclear cells from the peripheral blood of 20 patients with histologically and immunologically defined chronic lymphocytic leukemia of the B cell type (B-CLL) and 20 healthy individuals of various ages were investigated with T cell-specific monoclonal antibodies (OKT 4 and OKT 8) with regard to their subpopulation distribution. In B-CLL, a significant increase of lymphocytes reacting with OKT 8 could be demonstrated. Whereas there was a ratio of OKT 4 to OKT 8 of 1.72 in the control group, and OKT 4 to OKT 8 ratio of 0.67 was found in the B-CLL as a whole. With increasing clinical stage in accordance with the Rai scheme, a further displacement of this ratio in favor of OKT 8 positive cells was found. These results clearly show that, in peripheral blood of patients with B-CLL, an abnormal distribution pattern of circulating T cell subpopulations is present and that this also has prognostic relevance. (Author abstract) (24 Refs)

50. CIRCULATING IMMUNE COMPLEX LEVELS IN PATIENTS WITH GESTATIONAL TROPHOBLASTIC NEOPLASIA.

Rayner AA, Berkowitz R, Steele G, Schur PH, Rodrick ML, Goldstein DP, Harte PJ, Wilson RE, Zamcheck N, Munroe AE

(c/o Steele) Dept. Surgery, Brigham and Women's Hosp., Havard Medical Sch., 75 Francis St., Boston, MA, 02115

JNCI; 69(1):23-26 1982

The clinical course, human chorionic gonadotropin (HCG) levels, and serial circulating immune complex (CIC) levels in 21 patients with gestational trophoblastic neoplasia (GTN) were correlated for the evaluation of the relationship between CIC levels and trophoblastic tumor burden. CIC levels were normal in 18 of 21 patients at the time of presentation, and 2 of the 3 patients who presented with elevated CIC levels had significant comorbid disease (toxemia and hepatitis). Nine patients were followed into gonadotropin remission, and all nine developed an increase in CIC levels at the time of remission. It was concluded that CIC, at least as measured by two antigen-nonspecific techniques, is generally not elevated at initial presentation in the patient with GTN; this lack of an elevation is probably due to marked tumor antigen excess. Thus the in vivo importance of CIC as a 'blocker' of host antitumor response at this stage is doubtful. After effective treatment as HCG levels return to normal, the demonstrated elevation in serial levels of CIC may reflect a return of adequate host immune response at a time of minimal tumor burden. (Author abstract) (16 Refs)

REVIEWS

51. FETAL AND ONCOFETAL ANTIGENS. REGULATORS OF IMMUNE REACTIONS.

McCluskey DR

Dept. Haematology, Royal Victoria Hosp., Belfast, Northern Ireland

Med Hypotheses; 8(6):627-634 1982

Cellular immune system, fetal and oncofetal antigens, and the maternal-fetal relationship is discussed. Neoplastic transformation is associatied with expression of neoantigens, which are capable of stimulating an immune response, but also with reexpression of fetal antigens which appear to activate a variety of specific and non-specific suppressor mechanisms. In pregnant females and patients with choriocarcinoma, peripheral blood lymphocytes inhibited DNA synthesis of normal lymphocytes thus suggesting that in pregnancy and patients with trophoblastic tumors, altered lymphocyte immunocompetence may play a role in survival of the fetus and neoplasm respectively. (44 Refs)

52. SURFACE MARKERS ON LEUKEMIA AND LYMPHOMA CELLS: RECENT ADVANCES.

Foon KA, Schroff RW, Gale RP
Biological Response Modifiers Program, NCI-Frederick Cancer Res. Facility, Building 560, Frederick, MD, 21701
Blood; 60(1):1-19 1982

Recent advances in immunology have led to important insights into leukocyte differentiation and the cellular origin of leukemia. It is now possible to precisely define stages of human lymphocyte and granulocyte differentiation utilizing highly specific monoclonal antibodies that define cell surface antigens in conjunction with more traditional markers such as surface and cytoplasmic immunoglobulin on B lymphocytes, sheep erythrocyte (E) receptors on T lymphocytes, and cytochemical staining of myeloid cells. Five major subtypes of acute lymphoblastic leukemia (ALL) are now recognized, including unclassified or null ALL, common ALL (cALL), pre-B-ALL, B-ALL, and T-ALL. Within the T-ALL subgroup, there is considerable heterogeneity based on the presence or absence of the E-receptor and various T-cell surface membrane antigens defined by monoclonal antibodies. Cells from patients with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and Sezary syndrome also can be classified by their reactivity with monoclonal antibodies. Acute myelogenous leukemia (AML) cells are generally classified by morphological and cytochemical features. Recently, monoclonal antibodies reactive with granulocytic and monocytic subtypes of AML have been developed. In addition to their utility in leukemia classification, monoclonal antibodies that identify leukemia associated antigens have also been used therapeutically. Monoclonal antibodies have been infused intravenously into patients with leukemia and lymphoma. They have also been used in vitro with complement to lyse residual leukemia cells from remission bone marrows removed from leukemia patients. These treated bone marrows were later reinfused into the same patients to 'rescue' them following high-dose chemotherapy and radiation therapy. (Author abstract) (203 Refs)

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